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THE VOLUME
of
THE BLOOD AND PLASMA
IN HEALTH AND DISEASE

By
LEONARD G. ROWNTREE, M.D.

and

GEORGE E. BROWN, M.D.

Division of Medicine
The Mayo Clinic and The Mayo Foundation
Rochester, Minnesota

With the Technical Assistance of

GRACE M. ROTH

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FOREWORD

Studies of blood volume give a new outlook on many problems which long were considered settled. These researches illustrate again the dictum of Francis Bacon in 1606 when, in his "Novum Organum," he inveighed against authority in learning and pointed out that in science nothing can ever be considered settled because while the facts may remain the same, the viewpoint is changing constantly. The pure science of today is the applied science of tomorrow.

W. J. MAYO.

PREFACE

The study of blood volume is essentially a clinical problem. It concerns the living, not the dead. It belongs almost exclusively in the province of clinical investigation. The pathologist is barred from such studies at necropsy because of the changes incident to death. Animal experimentation offers little because of our limited capacity to reproduce disease in animals. The physiologist may well participate in establishing the limits of normal and the influence of various physiologic processes. But the true opportunity, so far as studies of blood volume are concerned, is in the field of actual practice. Here it is possible, without injury or harm to the patient, to determine the nature and extent of changes in the volume of plasma and blood in various diseases, and to ascertain the rôle that these changes play in the symptoms and signs of various diseases and in their course and outcome. The responsibility for the development of this field lies wholly with the physician.

In the following pages we are presenting the evidence which has accumulated during the last few years relative to observations made with the dye method. We are attempting to show the value of the study of the blood volume and plasma volume in clinical medicine. In this connection we wish to go back a few years and consider the introduction to the original paper (Keith, Rowntree, and Geraghty) on the dye method in which was sketched the manner by which studies of blood volume might bear on clinical problems:

“Routine erythrocyte counts and hemoglobin determinations yield information which is valuable but incomplete. This information concerns only the concentration of the blood. The routine methods do not furnish total values for circulating

hemoglobin, or circulating erythrocytes. With them, anemia may be more apparent than real, as it may be dependent on or associated with marked increase in plasma volume, whereas polycythemia does not necessarily indicate total increase in erythrocytes, as it may be dependent on a decrease in plasma. In order to obtain total values for either erythrocytes or hemoglobin, data relative to plasma volume or total blood volume are essential.

“The volume as well as the concentration of the blood must play a part in pathologic physiology. Total values are essential to the proper interpretation of certain pathologic data. Is an increase in the blood mass, with overfilling of the vascular system, in any way responsible for hypertension? Is the large heart frequently seen in pernicious anemia due to large blood volume? Is the large heart sometimes seen in myocardial insufficiency (unassociated with hypertension or nephritis) due to an increase in blood mass? Questions such as these must remain unanswered until data concerning total values are correlated with pathologic data.”

It is our belief, based on considerable experience, that the three questions presented in the original paper are answered satisfactorily. Many other questions that have arisen have been investigated, and in our opinion have been answered through the medium of the dye method of determining blood volume and plasma volume. Since accidents have not attended the use of the dyes, and untoward or toxic effects have not been noted in a series of more than 1,000 determinations, throughout a period of six years, we believe that fear of toxicity which is manifested by certain observers is entirely unwarranted. We believe that this method meets our clinical needs, that it is reliable, and that it has served the purposes responsible for its development and its introduction into medicine.

The value of studies of blood volume in clinical medicine is

difficult to determine accurately in the present state of our knowledge. So much doubt has existed concerning the reliability of the methods that the question of method has been constantly to the fore, and has tintured medical judgment. One might naturally inquire as to whether blood and plasma values have diagnostic, prognostic, and therapeutic significance in the management of the individual patient. The extent to which such studies will prove of service in these connections must be determined largely in the future. In the meantime, from the standpoint of the investigation of physiologic and pathologic variations in blood volume, the method provides a suitable measuring rod and already has yielded information of great value. In certain groups of diseases the deviation of the mean values from the means for normal persons provides much material for thought and further investigation.

The present seems to us a desirable time to discuss the status of blood volume studies, to review the literature on the experimental and clinical work carried out by the dye method, to consider the criticisms and suggestions offered by various investigators as to the results of their experience with this method, and also to present the results of our own clinical studies with this method, extending over a period of six years and involving more than 1,000 determinations in a series of more than 350 clinical cases.

We wish to express our gratitude to our colleagues of The Mayo Clinic for their interest and help—to Doctors Walter C. Alvarez, Hugo Ascanio, and Arnold Zimmermann for aid in the statistical material and to Doctors Norman M. Keith, Willis S. Lemon, Herbert Z. Giffin, Henry S. Plummer, and William A. Plummer for reference of patients for study, and to Doctors Carl H. Greene and Samuel Amberg for many kind suggestions.

LEONARD G. ROWNTREE.

GEORGE E. BROWN.

ROCHESTER, MINNESOTA,
November, 1929.

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The Volume of the Blood and Plasma in Health and Disease

Chapter I

INTRODUCTION OF THE DYE METHOD

The dye method of determining plasma volume and blood volume was introduced in 1915 by Rowntree, Keith, and Geraghty. The results of its application were published by Keith, Rowntree, and Geraghty in the same year. It involved a new principle: The direct introduction into the circulation of a known amount of a nontoxic, slowly absorbable dye. The dye remained in the plasma long enough for the two to become thoroughly mixed and its concentration in the plasma was determined colorimetrically by comparison with a suitable standard mixture of dye and serum. From the extent of the dilution of the dye the plasma volume was determined. The total blood volume was computed, utilizing for the purpose the hematocrit values obtained after rapid centrifugalization. By this method it was shown at that time that for normal man the plasma volume was approximately 5 per cent of the body weight (42 to 56 c.c. for each kilogram) and the total blood volume 8.8 per cent of the body weight (79 to 99 c.c. for each kilogram). Duplicate determinations on normal subjects were found to yield approximately identical values. Loss of blood following rapid bleeding and the increased volume immediately incident to infusion with blood

and physiologic sodium chloride solution were found to be fairly accurately reflected by this method. Increased blood volume and plasma volume in relation to body weight were encountered in the late stages of pregnancy and decreased volumes were discovered in obesity. It was found that changes in blood volume did not bear any significant relationship to hypertension. Constant or significant changes in blood volume were not found in anemia or in the anasarca accompanying myocardial insufficiency. Many of the values established tentatively by Keith, Rowntree, and Geraghty in 1915 have been replaced in subsequent work.

During the last decade this method has been employed by numerous investigators both in clinical investigation and in animal experimentation. It has been subjected to rather searching criticism. Certain steps in the method have been questioned and changes in technic have been suggested. Other substances, dyes or colloids, have been advocated as substitutes for vital red, but the method appears to have survived. As a matter of fact, the dye method seems at present to constitute the most practical clinical procedure for determining the circulating plasma volume and blood volume, and it seems to be coming into general use. One reason for its increased popularity is found in the fact that the carbon monoxide method, its only true competitor as a practical clinical method for determining blood volume, has also been subjected to question. The rôle of myohemoglobin in the carbon monoxide method is still unsettled, and this renders the interpretation of data unsatisfactory. Furthermore, in the recent Peruvian expedition⁷ for the study of effects of altitude the carbon monoxide method was discarded since it indicated marked changes in blood volume with changes in environmental temperature. This observation was later corroborated by work carried on in a glass respiration chamber in the Cambridge Physiologic Lab-

oratories.⁸ This showed that with this method blood volume increased as environmental temperature was raised. It is evident, therefore, that in all studies involving the use of the carbon monoxide method, environmental temperature must be considered. Further difficulty with the method was revealed by Barcroft and Barcroft, who demonstrated that the blood of the splenic spaces failed to keep pace with the peripheral blood in carbon monoxide saturation. When the hemoglobin of the splenic pulp, in rats breathing 0.06 to 0.1 per cent of carbon monoxide, is compared with the hemoglobin of the general circulation, there is a lag in saturation of the former which may attain thirty minutes. A similar lag, attaining ninety minutes, was demonstrated in the splenic blood of rats during the process of ridding the body of carbon monoxide.

On the clinical side, an analysis of the blood volume data for man, obtained with the carbon monoxide method as it appears in the literature, fails to inspire confidence. Thus from Erlanger's table we find the low values of 2.6 per cent for women and 3.9 per cent for men (Oerum⁸³); and we find, also, the high values of 8.8 per cent (Douglas, Haldane, Henderson, and Schneider). Obviously, these variations are entirely too large for the normal subject and must be due to defects in the method itself or to faulty technic. Neither in the older literature nor in the more recent work on blood volume do we find evidence which would encourage us to utilize the carbon monoxide method in conjunction with the dye method.

Attention is called to these facts not with the idea of disparaging the use of the carbon monoxide method, but rather to indicate that it also is not above criticism. A careful survey of the field of blood volume investigations brings to light some interesting considerations. Perhaps no single communication on the subject indicates a more comprehensive viewpoint and less biased opinions than the critical collective review of

Erlanger in 1921. He has subjected to critical analysis all blood volume methods and has discussed the principles involved and the technical modifications suggested. He has expressed his opinion frankly in relation to all these matters. He has considered the results obtained for various animals by various authors who have used various methods and he has attempted to correlate these observations. He has scrutinized not only the data obtained by each method, but also the basis for this or that suggestion for modification in technic. In many instances he has assailed the objection of critics, has questioned their data, and has assailed their interpretations of their own work.

From our study of the problem, extending over a period of several years, from a review of the literature, and also from consideration of Erlanger's review, we are convinced that there is not, as yet, an ideal method for the determination of blood volume. Nevertheless, we believe that in the dye method we have a practical procedure of great clinical importance. Despite all that has been written concerning discrepancies in mixing curves, unreliability of hematocrit readings, errors in colorimetric determination, and of the existence of extensive reservoirs for erythrocytes in liver or spleen (all of which are problems of practical as well as of academic interest), changes in blood volume are revealed by the dye method in many diseases. It would seem, therefore, that this method warrants general acceptance.

THE RELATIVE VALUE OF CERTAIN DYES AND OTHER COLLOID SUBSTANCES

In the original study vital red was employed, since it seemed to be the most suitable dye available. Its selection came about in the following manner: One of us (Rowntree) conceived the idea that following its intravenous injection and

after thorough mixing in the body, the extent of dilution of a known amount of a slowly absorbable dye might be employed as the basis of determining blood volume. Consequently Dr. H. M. Evans was consulted because of his large experience with vital dyes, and the large collection of dyes in his possession. At this conference it was decided that a nontoxic, nonirritant, slowly absorbable colloid dye of high tinctorial properties would meet our needs best. Several dyes were submitted to us with his opinion that of them all vital red would probably prove the most satisfactory. On actual trial this proved to be the case. As a result of these early studies a footnote was inserted in our paper: "It is probable that many dyes will answer the purpose equally well; studies along these lines are now in progress." A better dye was not found by us, but other dyes have since been suggested. Consequently, the relative merits of these various dyes warrant serious consideration, especially since vital red is not on the market and hence is not readily available.

Congo-red was suggested as a substitute by Harris in 1920. He claimed for it greater availability and slower disappearance from the blood stream. It has since been advocated by Griesbach, in 1921, and has come into general use. Dawson, Evans, and Whipple made a comprehensive study of the problem and found approximately thirty dyes possessing the qualities essential for estimation of blood volume. They preferred certain blue dyes, since they claimed that these dyes leave the blood stream more slowly, that blue colors can be read more accurately, and that blue does not obscure hemolysis. Their first choice was a blue azo dye (T1824) which has proved most satisfactory in their investigations on dogs, but has not been used in man. In their studies they used various samples of vital red dyes, comparing them all with the "original Rowntree dye." However, in most of the work of Whipple and his collaborators on blood

volume, brilliant vital red was employed. Instead of an artificial dye, hemoglobin itself has been suggested and has been tried in animals by Franke and Benedict, and from their results we believe that it also should prove quite satisfactory.

Substances other than dyes were employed in earlier years. Homologous blood of different erythrocyte content was tried, but this involved rather intricate calculations. Dextrin has been injected and dextrin dilution has been determined polarimetrically. Antitoxin has been used, and its dilution has been determined biologically; and foreign serum has been employed and its dilution has been studied quantitatively by precipitin reactions. Injections of isotonic glucose solution and physiologic sodium chloride solution also have been employed. None of these methods has proved reliable or practicable. Meek and Gasser have used gum acacia as an intravenous colloid, and have determined gravimetrically at the end of three minutes the amount of gum acacia in a known volume of blood. This work was based on Bayliss' employment of gum acacia in the treatment of surgical shock. This procedure yielded values closely approximating those of vital red, and proved quite satisfactory in practice. McQuarrie and Davis have injected a noncoagulable highly refractive substance, gum acacia and gelatin solution, and have noted the change in the refractive index as the result of dilution. This also yields values similar to those of the dye method.

It would seem, therefore, that there are many substances, colloids, and dyes which, on injection, yield dilution values of the same order of magnitude, and that any of these substances may be employed. Obviously, then, the question becomes one of availability and practicability. The dyes have an advantage in that they readily admit of colorimetric determination, and hence they have come into more general use.

In our own studies we are now employing Congo-red almost

exclusively. Long experience with both vital red and Congo-red led us to believe that they may be used interchangeably. In fact, Congo-red probably yields a color slightly more satisfactory from the standpoint of colorimetric readings. But its chief advantage consists in the fact that it is readily available.

THE FATE OF THE DYE INJECTED INTRAVENOUSLY

This subject has been studied in dogs by H. P. Smith,⁹⁶ who used brilliant vital red. It was found that the dye was slowly eliminated by the liver into the bile and that it did not appear in the urine. Not more than 25 per cent appeared in the bile within twenty-four hours. Much of the dye, on leaving the blood stream, is stored in the tissues, particularly in the reticulo-endothelial cells of the liver, spleen, and lymph-nodes, and in the epithelial cells of the kidney. Subsequently it is eliminated. From his experiments he concluded that about 12 per cent of the dye is lost from the circulation in the first hour and possibly 4 per cent between the fourth and tenth minute after injection. We do not believe that the possibility of actual destruction of the dye in the body has been given sufficient consideration. Smith's observation that dye is found in the lymph in considerable amounts is significant since it indicates that some lymph may be included in the blood volume as it is determined by the dye method. The amount, however, must be small, since only 12 per cent of the dye leaves the blood stream in one hour, while the test is made in from three to six minutes following the injection of dye. Smith suggested the possibility that the dye leaves the blood stream by means of diffusion as well as through phagocytosis by macrophages.

Chapter II

CRITICISM OF THE DYE METHOD

We believe that the criticisms which have been made against the dye method should be presented and considered. Consequently we shall discuss them in detail, presenting the adverse statements as they have appeared in the literature and giving, at the same time, our own data which bear on the subject.

ADSORPTION OF DYE BY THE BLOOD CELLS

Adsorption of dye by the blood cells was duly controlled and our evidence relative to the lack of adsorption for vital red was presented in our original publication.⁶⁴ Our ability to determine blood volume accurately in vitro and our failure to recover vital red from the cells by repeated washing demonstrated that the loss of dye in this way is entirely negligible. Whipple and his co-workers amply corroborated our observations in this respect.

Recently Lindhard⁷¹ has objected to the use of Congo-red on the ground that it is taken up in considerable amounts by the erythrocytes and is held in the insoluble stroma. After carefully repeating his experiments we did not find evidence that this holds true for the Congo-red which we employ.* Only when the dye is employed in concentrations of twenty to

* We have used with entire satisfaction the American dye obtained from the open market. Each lot is tested for toxicity in animals. From Lindhard's experiments it would seem probable that various samples of Congo-red may vary in adsorptive properties. On no other basis can we explain the discrepancy between his results and ours.

forty times that used in the clinical method could any trace of adsorption be demonstrated. The evidence for these statements will be found in the following experiments:

Experiment 1.—Blood from patient five minutes after injection of Congo-red for determination of blood volume:

(a) Two tubes (10 c.c.) were washed with 100 c.c. physiologic sodium chloride solution.

(b) Washed cells were hemolyzed and were washed five times with water to obtain insoluble stroma.

(c) Extracted with ether: Color was not present (contrary to statement of Lindhard for the Congo-red which he used).

Experiment 2.—Four tubes of cells from a patient with polycythemia vera:

(a) Two tubes before injection of Congo-red. Two tubes after injection.

(b) All four tubes hemolyzed with water and washed until only insoluble stroma remained.

(c) This was extracted with ether; color not present. On adding normal hydrochloric acid (which would turn Congo-red to blue) blue was not noted.

(d) A difference was not noted between tubes taken after injection of Congo-red and the controls taken before the administration of the dye.

Experiment 3.—Five cubic centimeters of cells in each of three tubes:

(a) One c.c. of 1.5 per cent solution of Congo-red, vital red, and Congo-rote was added to tubes 1, 2, and 3 respectively. The solution and blood were mixed and centrifugalized, and the cells then were hemolyzed.

(b) There was color in the stroma in all three tubes, with some gelatinous formation in the tubes which contained Congo-red. The gelatinous mass held some color which turned blue

on the addition of normal hydrochloric acid. This concentration was 160 times greater than that used by Lindhard in his experiments.

Experiment 4.—Three samples of blood of 5 c.c. each:

(a) To the first tube 0.25 c.c. of 1.5 per cent solution of Congo-red was added.

(b) To the second tube 0.25 c.c. of 1.5 per cent solution of Congo-rote was added.

(c) To the third tube 0.25 c.c. of 1.5 per cent solution of vital red was added.

On hemolyzing the blood and adding ether, color could not be extracted after six washings. On the addition of hydrochloric acid, blue could not be detected. Dye could not be detected in the cells at this concentration. Lindhard used 0.3 c.c. of 1 per cent solution of Congo-red in 200 c.c. of ox blood, which is equivalent to 3 mg. in 200 c.c. of blood. In our experiments we used 3.75 mg. in 5 c.c. of human blood, a concentration more than forty times greater than that used by Lindhard. Color could not be detected at this concentration in our experiment.

CONGO-RED AS AN INDICATOR

Lindhard⁷¹ has objected to the employment of Congo-red on the basis that it is an indicator, and hence useless from the standpoint of quantitative color determinations. Inasmuch as the range of hydrogen-ion concentration through which it changes color is from pH 3 to 5, and since the hydrogen-ion concentration of blood is pH 7.2 to 7.4 this criticism can be dismissed from further consideration. The salt and protein content of serum are not unfavorable to the Congo-red method, since the patient's serum is employed in the same amounts for both the test and the control.

THE CONCENTRATION CURVE FOR THE DYE AND VARIATIONS IN
THE MIXING CURVES

Another great problem connected with the dye method is the determination of the most satisfactory time after injection for the removal of blood for the determination of the plasma volume. Two factors are concerned: Allowance of adequate time for thorough mixing of the dye in the blood and determination of the extent of dilution of dye by the blood prior to any extensive loss of dye from the circulatory system. The optimal time for making the determination obviously is very important. Erlanger, in his discussion of this problem, presented a series of nine mixing curves constructed from data derived from published reports of different workers. The data are concerned with various methods: vital red, Congo-red, and solutions of gum acacia and sodium chloride. The concentration curves reveal considerable variations during the first ten minutes. In this connection we felt that more data were desirable, especially in regard to the use of vital red and Congo-red. Consequently, we conducted certain studies to show the optimal times for taking measurements. The concentration of the dye three, four, and six minutes after injection was determined in forty-six subjects, including twenty normal persons, seventeen patients with polycythemia vera, and nine patients with various types of anemia. The results were recorded in percentage variation from the concentration of the dye after two minutes, which arbitrarily was taken as 100 per cent. Table 1 shows that there is practically no difference in the readings after three, four, and six minutes; and it is obvious that collections made anywhere from three to six minutes after injection should prove satisfactory. This holds true for both normal and pathologic subjects.

TABLE 1

CONCENTRATION OF THE DYE IN NORMAL AND PATHOLOGIC SUBJECTS AT VARYING INTERVALS AFTER INJECTION*

	Twenty normal subjects.			Seventeen patients with polycythemia vera.			Nine patients with anemia.		
	3	4	6	3	4	6	3	4	6
Period (minutes).....	3	4	6	3	4	6	3	4	6
Determinations.....	20	19	18	17	18	15	9	9	6
Mean concentration* of dye (plasma), per cent.....	100.6 ±0.5	101.5 ±0.6	101.4 ±0.5	101.3 ±0.5	101.4 ±0.7	100.8 ±0.5	100.1 ±0.4	101.4 ±0.5	100.8 ±0.7
Standard deviations of distributions, per cent.....	3.6	3.7	3.0	3.0	4.1	3.0	1.9	2.1	2.6

* The concentration of the dye for the two-minute period is arbitrarily taken as 100 per cent.

Harris advocated that determinations be made at two to two and a half minutes after injection. Dawson, Evans, and Whipple, and Hooper, Smith, Belt, and Whipple favored determinations in from two to four minutes and claimed that 6 to 11 per cent of the dye was lost in twenty minutes and from 4 to 5 per cent from the fourth to the tenth minute. Smith's⁹⁶ results show that, on an average, 12 per cent of the dye is removed from the circulation during the first hour. Erlanger believed that the time for complete mixing in the blood is likely to be greater than that usually accepted. We believe that collections from three to six minutes after injection are best, and hence that departure from our original method is not desirable.

UNEVEN DISTRIBUTION OF ERYTHROCYTES AND PLASMA IN DIFFERENT BLOOD VESSELS

It has been objected by Lamson and Nagayama that: "None of our methods suffice for the determination of the true blood volume for the reason that blood is a suspension of corpuscles of constantly varying size in a fluid which is also undergoing variations in volume and that the concentration of the corpuscles is not the same throughout the circulation."

Erlanger said in reply: "These investigators do not present any new evidence indicating that variations of the kind mentioned are of sufficient magnitude to be the cause of our difficulty in determining the normal blood volume." Lindhard⁷² has also stated that the dye is not uniformly distributed throughout the body except under the influence of exercise. For the purpose of determining the soundness of these criticisms we have carried out seven experiments in which, following the injection of the dye, blood was taken simultaneously from the two arms, and blood volume determinations were made and the values compared (Table 2). A significant difference could not be detected in blood values when blood was drawn simultaneously from both arms under resting conditions.

TABLE 2

DETERMINATIONS OF THE BLOOD VOLUME AND PLASMA VOLUME MADE WITH BLOOD TAKEN SIMULTANEOUSLY FROM THE RIGHT AND THE LEFT ARMS

Condition of patient.	Volume, c.c.			
	Blood.		Plasma.	
	Right.	Left.	Right.	Left.
Normal.	5,600	5,580	3,360	3,350
Normal.	7,360	7,360	4,040	4,040
Polycythemia vera.	8,500	8,500	4,500	4,500
Polycythemia vera.	8,020	8,020	3,150	3,150
Polycythemia vera.	9,300	9,380	3,715	3,750
Edema of chronic glomerulonephritis. . .	3,660	3,500	2,420	2,380
Banti's disease.	8,300	8,300	5,800	5,800

A repetition of Lindhard's work immediately revealed a technical difficulty which may suffice to explain his results

Venipuncture and withdrawal of blood from the superficial vessels of the legs, within the time limits prescribed, frequently is impossible. Unless the vessels are readily entered and the blood flow is easy and rapid, errors will creep in. In every instance in which simultaneous withdrawal of blood from the median cephalic and basilic veins of the arm and the veins of the ankle was attempted, the withdrawal of blood from the vessels of the leg was relatively slow. This we believe to be sufficient to vitiate the results. Indeed in several instances more than five minutes were required for the withdrawal of an adequate amount of blood from the external saphenous vein, whereas in every instance the same amount was withdrawn from the median cephalic and basilic veins within thirty seconds. When the flow of blood is so slow that considerable suction is necessary, the plasma and cell relationships readily may be modified, and may result in distorted readings of blood volume.

We have no data concerning the blood of the deep vessels or of the portal circulation. Our studies satisfied us that the erythrocytes and the dye are fairly evenly distributed throughout the blood or, at least, that uneven distribution, if it exists, does not interfere with the constancy of the figures expressive of blood volume as evidenced by repeated determinations in the same subject. The results, furthermore, of our studies of blood which was obtained simultaneously from both arms constitute valuable evidence of even distribution of the dye.

EXERCISE

Lindhard⁷² claims that exercise is necessary for thorough mixing of the blood and that consequently blood volume values are acceptable only during or immediately after exercise. He estimated blood volume from specimens of blood obtained respectively from the median basilic and from the saphenous veins. While the patient was resting and sitting, he obtained,

with blood from the median basilic vein, values for total blood volume of 4.7 liters, and while the patient was walking and exercising, values of 2.8 liters. With blood from the saphenous vein, the corresponding values were 7.25 and 2.8 liters, respectively.

Lee, Carrier, and Whipple studied the effects of exercise on the blood volume, using in their work the combined method of dye and carbon monoxide. After dogs had experienced periods of exhausting muscular exertion there was no sign of maintained or constant effects on the plasma volume. Broun,^{18, 19, 20, 21} on the other hand, employing the dye method, found values indicative of considerable increase of plasma volume and a decrease in the cell volume and total hemoglobin in sedentary animals after prolonged periods of exercise. He adduces marked destruction of blood as the explanation.

All of our blood volume determinations have been made with the patient at rest and in the prone position, thus obviating effects of gravity on the concentration of the venous blood. We have obtained duplicate determinations which check satisfactorily in a score of cases, and have not seen any difference in the blood volume values as determined simultaneously from both arms. We are satisfied, therefore, that with the dye method it is possible to obtain consistent and reliable results with the patient at rest.

In our routine experiments, the subjects did not exercise, since we felt that exercise might introduce complicating factors and make comparable determinations difficult. Furthermore, many bedridden patients cannot be subjected to exercise. At present, as the result of Lindhard's work, one is justified only in raising the question of whether or not exercise may affect the mixing of the dye in the blood, or the blood volume values. From Whipple's work on dogs this seems unlikely. White's studies in animals support Whipple's point of view. The prob-

lem must be investigated further. Our data, however, are of plasma volume and blood volume under basal conditions. Standards for blood volume during or after graded exercise have not as yet been established. In the event that exercise should be shown to affect blood volume values, this would in no way nullify the value of work dealing with blood volume during rest and under basal conditions.

BODY POSTURE

As a result of the suggestions contained in one of Lindhard's papers, Thompson, Thompson, and Dailey have carried out studies on "The effect of posture upon the composition and volume of blood in man." Early in their work they observed certain changes in concentration which appeared when the subject assumed the "standing still" position and they believed these changes to be occasioned by the assumption of this posture itself. They suspected that a diminution was caused in the total amount of plasma. Carefully controlled experiments in the standing still position indicated for blood from the median basilic vein (1) an increase in the number of erythrocytes for each cubic millimeter of blood; (2) a corresponding increase in the volume of cells for each liter of blood; (3) an increase in the specific gravity of plasma; (4) an increase in the concentration of plasma-proteins; (5) a decrease in the concentration of plasma-water, and (6) a decrease in the total amount of plasma in the blood of the whole body. On resumption of the recumbent position, the values are reversed. These observations they interpret as indicating a net loss from the blood of approximately protein-free fluid in the standing still position. They believe that the loss is due to increase in capillary pressure, and that it approximates, after thirty minutes, about 11 per cent of the plasma volume.

Thompson, Alper, and Thompson studied, by means of

vital red, "The effect of posture upon the velocity of blood flow in man" and found that a much longer time is required for blood to move from a vein in the arm to a vein in the foot, or the reverse, in the standing still position than in the recumbent position.

Besides the interest attaching to the results of these studies themselves, this work further demonstrated the necessity of determining blood volume under constant conditions. Our studies have been carried out, as a routine, under basal conditions, with fasting patients in the supine posture, after a preliminary period of rest of not less than twenty minutes.

THE RELIABILITY OF HEMATOCRIT READINGS

Although many observers are willing to accept the dye method as reliable for the determination of plasma volume, they object to our method of computing the total blood volume from figures based on hematocrit readings; in fact, a widespread prejudice against the hematocrit method has arisen, with an inclination to question the reliability of all such readings. Our actual experience with 350 cases and with more than 1,000 determinations of blood volume and with a long series of such readings carried out in quadruplicate, leads us to believe that they are sufficiently reliable for all practical purposes. Five cubic centimeters of blood in a 15 c.c. accurately graduated centrifuge tube is centrifugalized for thirty minutes at 3,000 revolutions a minute, always in the same centrifuge. The volume of the corpuscles is expressed as a percentage of the volume of the sample of blood drawn. With the so-called dry method, in which coagulation is prevented by the addition of 1.6 mg. of dry oxalate, the average cell volume is 40.8 ± 0.4 per cent. The standard deviation or mean variation from the average value for one series of 133 quadruplicate estimations by which results in this paper were verified was 1.5 per cent (of the total

blood in the centrifuge tube), which is not a large or a serious variation.

It should be noted at this point that Whipple and his associates have shown that the use of dry oxalate causes shrinkage of the corpuscles and gives readings lower than they should be; to obviate this, they add 2 c.c. of 1.6 per cent solution of sodium oxalate to each 10 c.c. of blood, a solution practically isotonic with blood. We have made duplicate "wet" and "dry" estimations on ninety-three subjects and have found, as did Whipple and his associates, that with the wet method the corpuscle volumes average 3.4 per cent (of the volume of blood in the tube) higher than with the dry method. The range was from -1.6 to $+9.6$ per cent, and the standard deviation was 2.4 per cent calculated as per cent of the volume of blood in the tube. We have also used the wet and dry methods in studying normal dogs.

As the result of these studies based on Whipple's criticism, we have carried out certain other experiments designed to settle this question. The hematocrit readings were taken, by both the wet and the dry methods, on blood from a heparinized dog. Previously, 1 mg. of heparin for each kilogram of body weight was given intravenously. This rendered the blood incoagulable and enabled us to dispense with sodium oxalate entirely in one series of readings. The hematocrit readings were then determined in three series of experiments: (1) The heparinized blood alone was used; (2) the wet method on the heparinized blood, and (3) the dry method on the heparinized blood. The results clearly indicate that the wet method is to be preferred (Table 3). It is also evident that the shrinkage of erythrocytes of dogs when dry oxalate is used is more marked than is the same phenomenon in man under parallel conditions. As the result of these studies, we accept Whipple's⁵⁹ criticism of the dry oxalate technic, and we now have adopted his pro-

cedure involving the use of 1.6 per cent sodium oxalate solution. In our work with the dry oxalate method we have made the necessary correction for the shrinkage of cells.

TABLE 3

COMPARISON OF HEMATOCRIT READINGS ON BLOOD TREATED IN DIFFERENT WAYS

	Tubes.						Mean.	Comment.
	1	2	3	4	5	6		
Results with heparinized* blood to which oxalate was not added, per cent.	35.7	35.7	35.1	35.8	35.7		35.6	
Results with heparinized blood to which oxalate solution was added, per cent.	35.6	35.6	35.6	35.5	36.7	35.1	35.7	Tubes contained 1 c.c. of 1.6 per cent solution of sodium oxalate.
Results with heparinized blood to which dry oxalate was added, per cent.	29.7	28.6	29.7	31.7	31.5	29.6	30.0	Tubes contained 1 c.c. of 1.6 per cent solution of sodium oxalate dried in a sand bath.

* The dog was given intravenously 1 mg. of heparin for each kilogram of body weight.

In connection with this correction for cell volume, another problem is presented, namely, whether or not this shrinkage of cells occasioned a relative increase in plasma and caused an undue dilution of the dye. This would give an excessive value for blood plasma. An experiment on a normal subject devised to control this possibility showed for plasma 3,075 c.c. by the dry method and 3,070 c.c. by the wet method, and for total blood volume 4,520 c.c. by the dry method and 4,660 c.c. by the wet method; that is, no significant difference in the values for plasma and a somewhat smaller (3 per cent) rather than a larger value for the total blood by the dry method. That the possibility must still be considered, however, is evidenced by similar studies carried out in two cases of our series of polycythemia. In these cases the average plasma volume by the dry method was greater by 5 per cent, although the increase

in the total blood volume was only 2 per cent greater for the dry than for the wet method. Inasmuch as this evidence is not entirely clear we believed it wiser not to attempt any correction for plasma values. It must be admitted that our values for plasma volume may be slightly higher than normal. From the foregoing statements it is quite obvious that this wet method is the method of choice and, as we have already stated, it is the method we now employ.

SAFETY IN THE USE OF THE DYE METHOD

Obviously, it is important to make sure that the dye method is safe. In the original presentation of the method⁶⁴ we said: "Aside from the slight pain of the venipuncture, the patient usually does not suffer from discomfort or inconvenience. In approximately 9 per cent of the cases, chilly sensations occurred, while in five, chills with fever reaching 101° were noted. In none of the normal cases was there thermal response. Reactions are apparently more common in cases of anemia." Apparently fear of vital red was a factor in the minds of Barcroft and his associates,⁷ who stated: "We did not use vital red to check our carbon monoxide results as we heard of two human cases in which injection of this material proved all but fatal. It would appear that some samples of this pigment may be more toxic than others or some persons more susceptible to it." Against this statement must be placed the fact that in the last six years, during which we have made hundreds of determinations on sick and well subjects, we have not observed toxic effects in a single instance. We are inclined, therefore, to ascribe our earlier difficulty with reactions, chills, and rise of temperature to technical matters pertaining to intravenous injections, distilled water, rubber tubing, and so forth. With modern intravenous technic we do not have any apprehension with regard to reactions from the use of the dye.

RELIABILITY AND PROBABLE ERROR OF THE DYE METHOD

It is extremely difficult to determine errors in the dye method with any degree of certainty since there is no accepted or authentic standard for blood volume and plasma volume with which to compare the results obtained by the dye method. Consequently we are forced to rely on indirect evidence and to emphasize: (1) The constancy and reduplication of the results obtained by the dye method in the same subject on repeated determinations; (2) the results of *in vitro* measurements of the plasma and whole blood; (3) the extent of technical errors in certain steps in the method, and (4) the variations from normal which in certain diseases are fairly constant for each disease.

The results of two determinations of plasma volume made on nine normal men by Keith, Rowntree, and Geraghty show an average variation between the two determinations of 1.5 per cent. We have carried out repeated determinations of blood volume in twelve normal subjects over periods of two to fourteen days, with an average variation of only 5.8 per cent, whereas in ten cases in which determinations were repeated after one to twenty-four months, the mean variation was 8.6 per cent. We believe, however, that the variation over this long period does not necessarily represent error of the method, but that in many instances physiologic fluctuation of approximately this magnitude actually has occurred. Repeated determinations of blood volume in five dogs, at short intervals of one to two hours, showed an average variation of 1.3 per cent. In determination of blood volume using blood withdrawn simultaneously from the right and left arms there was an average variation for seven subjects of 0.7 per cent. It is obvious, therefore, that criticism cannot be raised against the method on the basis of inconstancy of determinations in the same subject.

In vitro studies, undertaken in 1915⁶⁴ to ascertain whether adsorption of the dye by the erythrocytes occurred, showed a mean difference between calculated and observed values of less than 1.2 per cent. Whipple's⁵⁹ in vitro studies of blood volume, undertaken to determine the accuracy of the method, resulted in striking evidence in its favor. He mixed blood in vitro with the dye and then determined the percentage of cells by the hematocrit. The actual plasma volume in one experiment as indicated colorimetrically was 455 c.c. and the amount indicated by the hematocrit was 465 c.c. In a second experiment the actual plasma measured 115 c.c. and the amount indicated by the dye was 121 c.c. In repetition of this experiment, using Congo-red instead of vital red, we obtained a value of 463 c.c. for dye dilution against the hematocrit value of 465 c.c.* It would seem, therefore, that so far as in vitro experiments are concerned, the extent of the dilution of the dye in blood is an accurate index to the volume of plasma which is present.

A study of the mixing curve in twenty normal persons at three-minute, four-minute, and six-minute periods showed an average variation from that at two minutes of only 1.5 per cent. For forty-six persons (Table 1) including normal subjects, patients with anemia, and patients with polycythemia vera, the average variation, compared with the concentration after two minutes of mixing, was less than 1.5 per cent. Hematocrit readings were made in quadruplicate in 133 determinations of blood volume with an average deviation from the mean of 1.5 per cent (page 33). Consequently it is evident that the individual steps involved in the technic employed are not subject

* In our experiment the hematocrit value was 53.5 per cent for cells and 46.5 per cent for plasma. On the basis of the plasma volume and the hematocrit value the total blood volume would be 996 c.c. as against the actual 1000 c.c.

to serious criticism. The only desirable change from the original technic that is of any real consequence was that indicated by Whipple, relating to the shrinkage of erythrocytes incident to the use of dry oxalate as an anticoagulant.

Finally, it will be shown (Chapter V) that normal persons of standard height and weight in relation to age show rather constant blood volume for the group as a whole. Certain patients consistently show marked variations from normal. Thus numerous determinations on patients with polycythemia vera (Chapter VIII) revealed blood volume values of two to three times the mean value for normal persons, with return to strictly normal values following administration of phenylhydrazine. Myxedema, on the other hand, shows volume values for each kilogram of body weight of 20 to 25 per cent below the mean as established in this paper. From the evidence presented, it is clearly indicated that the dye method yields results that are at least consistent so long as the conditions are constant. It can thereby be regarded as a reliable index to the actual circulating blood volume and plasma volume. The error, so far as constancy of results is concerned, is probably not in excess of 5 per cent, which is fairly accurate for clinical tests in general. It may be argued that all values by this method are too high and that its use results in continual exaggeration of the amount of circulating plasma and blood. We believe that the burden of proof rests on those who make this assumption.

For the reader's convenience we are including a modification (Table 4) of a table presented by Erlanger which gives the observations of the blood volume in various animals, and in man by various workers using various methods. It emphasizes the extent of variations as represented by various workers for the same and for different methods.

TABLE 4

BLOOD VOLUMES AS DETERMINED BY VARIOUS METHODS (TAKEN FROM ERLANGER'S TABLES)

Sub- ject.	Method.	Cases.	Weight.		Mixing time, min- utes.	Blood weight Body weight	
			Range, kg.	Aver- age, kg.		Range, per cent.	Aver- age, per cent.
Man	Washout.....	2				7.2- 8.2	7.7
Man	NaCl-hematocrit .	4	52.5 -64.0	58.8	4-5	7.7- 8.7	8.3
Man	NaCl-colorimeter .	5	54.4 -67.5	58.0	0-3	4.7- 5.8	5.2
Man	NaCl-refraction...	19	49.0 -75.0	62.6	4	6.3- 8.4	7.4*
Man	Glucose-NaCl. . .	3	41.3 -60.1	53.6	5-10	5.1 - 5.9	5.5*
Man	Carbon monoxide..	14	58.2 -89.0	72.2	2-3	3.3- 6.3	4.8
Man	Carbon monoxide..	4	65.0 -77.0	70.3	3-4	5.0- 6.0	5.6
Man	Carbon monoxide..	9	76.5 -57.0	65.9	?	3.9 - 8.8	5.5*
Woman	Carbon monoxide..	3	44.0 -75.0	60.3	?	2.6 - 7.0	4.9*
Woman	Carbon monoxide..	6	44.0 -70.0	57.0	?	4.6 - 6.4	5.6*
Man	Carbon monoxide..	{ 1 1	65.0 70.0		+ +	7.57 8.43	{ 7.6* 8.4* }
Man	Carbon monoxide..	{ 4 4	51.6 -79.5 51.6 -75.9	66.3 63.9	20 20+	6.3 - 8.3 7.7 - 8.8	{ 7.3* 8.3* }
Man	Carbon monoxide..	6	72.7 -60.9	65.4	±10	5.5 - 7.4	6.8*
Man	Carbon monoxide..	20	6-16 yrs.		+	6.1 - 8.2	6.9
Man	Antitoxin.....	9	38.5 -83.0	58.1	?	5.9 -10.2	8.7
Man	Antitoxin.....	9	52.0 -88.7	67.2	15	8.9 -10.7	9.8
Man	Antitoxin.....	10				5.7 - 9.1	7.9
Man	Vital red.....	18	76.3 -47.4	60.4	3-6	8.2 -10.4	8.8
Dog	Washout.....					7.1 - 8.9	
Dog	Washout.....	1	2.47				7.9
Dog	Washout.....	2	0.79 -1.46			8.7 - 8.0	8.3
Dog	Washout.....	2	1.85 -4.23			8.9 - 8.4	8.6
Dog	Washout.....	1	3.1				7.9

* The relation of blood content to body weight by some investigators (see bibliography accompanying Erlanger's article) is expressed as the ratio of blood volume in c.c. to body weight in grams; by others, as the ratio of blood weight in grams to body weight in grams. Not infrequently it is impossible to determine which method is employed. We feel that the relation should be that of blood mass to body mass, i. e., of weight of blood to weight of body, and wherever the other method clearly has been employed, we have taken the liberty of making the conversion by multiplying the figures by 1.056. The asterisk (*) indicates the figures so derived.

TABLE 4—*Continued*

BLOOD VOLUMES AS DETERMINED BY VARIOUS METHODS (TAKEN FROM ERLANGER'S TABLES)

Sub- ject.	Method.	Cases.	Weight.		Mixing time, min- utes.	Blood weight Body weight	
			Range, kg.	Aver- age, kg.		Range, per cent.	Aver- age, per cent
Dog	Washout.....	3	0.40- 0.45			5.6 - 6.1	
Dog	Washout.....	2	11.5 -15.6			6.9 - 6.9	6.9
Dog	Washout.....	1	4.9				8.2
Dog	Washout.....	5	2.35- 6.18	4.25		7.0 - 9.9	8.3*
Dog	Washout.....	61	8.0 -39.5	20.3		4.7 - 8.6	6.8
Dog	Washout.....	3	5.78-10.35	8.61		7.8 - 8.7	8.2
Dog	Carbon monoxide..	9	10.1 -20.3	18.8	15	7.7 - 9.7	8.6*
Dog	Carbon monoxide..	4	5.7 -11.5	9.7	?	7.4 - 9.5	8.4
Dog	Vital red.....	22	7.3 -22.0	15.1	4	8.9 -12.1	10.6*
Dog	Vital red.....	4	6.0 - 9.7?	?	4?	8.4 - 9.4	8.9
Dog	Congo red.....	6	4.7 -16.5		?	7.0 - 8.2	7.6
Cat	Washout.....	1					6.9
Cat	Washout.....					4.6 - 4.8	
Cat	Vital red.....	2	3.8		?	6.0 - 6.6	6.3
Cat	Congo-red.....	3	1.7 - 3.0		?	5.5 - 5.5	5.5
Cat	Gum acacia gravi- metrically.....	8	1.5 - 4.3	3.04	10	4.5 - 6.8	5.5

* *Ibid.*

THE COMBINATION METHOD OF DETERMINING BLOOD VOLUME:

BY THE DYE METHOD FOR PLASMA VOLUME AND THE CARBON
MONOXIDE METHOD FOR ERYTHROCYTE VOLUME

Lamson and Nagayama, doubting the observations from the dye method for total blood volume, have developed a method of calculation which they designate the "true blood volume." The plasma volume values obtained with the dye method are combined with the erythrocyte volume values determined by the carbon monoxide method. In this connection Erlanger

asserted: "These investigations do not present any new evidence indicating that unequal distribution of cells and plasma in various parts of the body is of sufficient magnitude to be the cause of our difficulty in determining the normal blood volume. . . . They merely assume that because vital red, which is diffused through the plasma, indicates a blood volume in man of 8.8 per cent of his body weight and that because carbon monoxide, which is carried by the erythrocytes, indicates a blood volume (in the hands of some investigators) of 5.5 per cent, therefore the former determines the plasma volume and the latter the volume of corpuscles floating in that plasma. On this basis they developed a method of arriving by calculation at the true blood volume. But why adopt 5.5 per cent as the blood volume by the carbon monoxide method when others get figures as high as 8.4 per cent? While admitting the soundness of their underlying argument, it has yet to be demonstrated that, excepting possibly under certain very abnormal conditions, the two types of blood volume methods necessarily give inconsistent results, and if they do, that the discrepancies are due to uneven distribution and uneven size of the red cells."

On the other hand, after prolonged study of the blood volume of dogs, Whipple⁹⁷ concluded that the combined method should be employed, that the dye method should be used for the study of plasma volume, and that the carbon monoxide method should be used for the determination of erythrocytes. But with the conclusion as to the necessity of combining the two methods in order to determine total blood volume we disagree entirely. Both Lamson and Whipple expressed their belief, based on animal experimentation, that the dye method yields the most reliable data obtainable with reference to plasma volume, and Lamson stated that if a single test of blood volume is to be employed at all, the dye method is as good as any, "if not actually the best in existence."

We believe, as the result of years of experience with the dye method, that it yields data of practical clinical significance, and we see no necessity in practice for combining the two methods in question. In Chapter I we have indicated the criticisms which have been raised against the carbon monoxide method. This method was in existence at the time our original work was undertaken, and we developed the dye method because we were convinced of the inadequacy of the carbon monoxide method. The washout method, as used by Welcker,^{109, 110} revealed a blood volume of 7.7 per cent. Any method which yields values less than this, such as 5.5 and 3.5 per cent, which have been reported by workers using the carbon monoxide method, is obviously at fault. Controls of every kind have been carried out in working with the dye method, and criticisms in the literature have been taken into consideration. These controls convince us that the error of the method is not greater than 5 per cent. Those who have had a great deal of experience with the carbon monoxide method have shown a striking lack of confidence and enthusiasm. All of our experience strengthens our belief that the dye method in itself yields reliable and valuable information, much more reliable than that obtained with the carbon monoxide method. Hence we believe that the dye method is the method of choice and that it alone should be used.

Chapter III

TECHNIC OF THE DYE METHOD

In the dye method of estimating blood volume a known amount of slowly absorbable dye is injected into an unknown amount of fluid and its dilution is determined by comparing it with a standard dye of known dilution.

PROCEDURE FOR DETERMINING BLOOD VOLUME

1. From our earlier work, carried out on normal subjects, we estimate for each kilogram of body weight approximately 50 c.c. of plasma. Therefore, a theoretically approximate volume can be assumed and utilized for purposes of comparison. If the weight is 50 kg., 50 multiplied by 50 c.c. equals a theoretic plasma volume of 2,500 c.c. By calculating the theoretic plasma volume and dividing by 200 (a factor determined by experiment), the number of cubic centimeters of the solution of dye to be injected is determined. This is measured and injected from a calibrated Record syringe.

2. A solution of 1.5 per cent vital red or Congo-red is used. It is made by dissolving 375 mg. of dye in 25 c.c. of fresh, triple-distilled water.

3. Four 15 c.c. calibrated centrifuge tubes are provided and 1 c.c. of 1.6 per cent solution of sodium oxalate is placed in each.

4. A needle is inserted in the vein of one arm and 10 c.c. of blood is taken; 5 c.c. is placed in each of two centrifuge tubes for standard plasma color. Without removing the needle from the vein, syringes are changed and the dye injected.

5. In three to six minutes 10 c.c. of blood is withdrawn

from the opposite arm and 5 c.c. is placed in each of the two remaining centrifuge tubes.

6. All four tubes are centrifugalized for thirty minutes at 3,000 revolutions a minute; the hematocrit readings then are taken. In any one institution the same centrifuge always should be used in making these determinations.

7. The standard and unknown are prepared for colorimetric comparison. The standard is prepared by mixing 2 c.c. of plasma without dye, 2 c.c. of 1 : 200 dilution of the 1.5 per cent solution of the dye as injected, and 4 c.c. of physiologic solution of sodium chloride. The unknown is prepared by mixing 2 c.c. of plasma containing the dye and 6 c.c. of physiologic solution of sodium chloride.

8. The reading of the standard of the colorimeter is set at 10 and the standard and the unknown are compared. With the wet oxalate technic the following calculation is carried out: The correction for the dilution by oxalate equals the total number of cubic centimeters of oxalated plasma present in the tubes containing the dye, minus 1, divided by the total number of cubic centimeters of oxalated plasma in the tube.

The formula then reads:

$$\frac{200 \times \text{number of c.c. of dye injected} \times \text{the dilution factor}}{\text{Per cent of the unknown expressed in per cent of standard}} = \text{Plasma volume (in c.c.).}$$

$$\frac{\text{Plasma volume (in c.c.)} \times 100}{\text{Plasma per cent (hematocrit)}} = \text{Whole blood volume (in c.c.).}$$

In certain diseases in which large plasma volume or large total blood volume is anticipated, 18 c.c. of the solution of dye is given irrespective of the weight of the patient, and this is taken into consideration in the final calculation.

Whipple⁵⁹ has used a modification of this method. He used a 1 per cent solution of brilliant vital red instead of vital red

or Congo-red. To determine the hematocrit value the wet method was employed by Whipple, that is, 2 c.c. of a solution of 1.6 per cent sodium oxalate for 10 c.c. of blood.

OUTLINE OF WHIPPLE'S MODIFICATION AS USED ON NORMAL DOGS

"A hypodermic needle is inserted into the vein and 10 c.c. of blood drawn (with as little compression of the vein as possible) into a dry well-vaselined syringe. The blood is immediately placed in a 15 c.c. graduated hematocrit tube containing 2 c.c. of a 1.6 per cent solution of sodium oxalate. The blood and oxalate are mixed by inversion and the tube stoppered. A standard amount of the dye is drawn up into a syringe along with 5 to 10 c.c. of 0.9 per cent saline. This dye solution is now injected into the jugular vein, the dye being washed completely out of the syringe into the blood stream by means of a few cubic centimeters of saline. The dye solution is 1 per cent strength and is given in the amount of 1 c.c. per 5 kilos body weight. This is the amount arbitrarily taken by us, but more or less may be used to suit individual taste in color readings.

"Exactly four minutes after the injection of this dye a clean needle is again inserted into the jugular vein (preferably of the opposite side) and another 10 c.c. sample of blood is drawn and placed in another hematocrit tube also containing 2 c.c. of 1.6 per cent sodium oxalate. The hematocrit tubes are now centrifugalized at 2,500 revolutions a minute for thirty minutes. The total contents of the tube and the number of cubic centimeters of blood cells are now noted. Two cubic centimeters of the dye-colored plasma are pipetted off and diluted in a small tube with 4 c.c. of 0.9 per cent sodium chloride. This unknown is then read in a colorimeter against a standard prepared as follows:

"1. Seventy-five hundredths cubic centimeter of 1 per cent

brilliant vital red is pipetted into a 200 c.c. volumetric flask which is then made up to the mark with distilled water.

"2. Five cubic centimeters of this aqueous dye solution are then diluted with 5 c.c. of clear dye-free plasma (obtained from the first sample of blood drawn from the animal) and 5 c.c. of 0.9 per cent sodium chloride, making in all 15 c.c. of standard dye solution.

"Against this standard the above unknown is read and expressed in per cent. This value will henceforth be referred to as *R*.

"Let us assign the following values to be used in the formula below:

"*D* equals the number of cubic centimeters of 1 per cent brilliant vital red injected into the animal.

"*C*, the correction for the dilution by oxalate present equals the total number of cubic centimeters of oxalated plasma present in the second sample of blood drawn, minus 2 divided by the total number of cubic centimeters of oxalated plasma present in the same tube. This value expresses the ratio between the actual concentration of dye in the plasma when diluted with oxalate solution to the value when not so diluted.

"*R* equals the observed colorimetric reading (in per cent of the standard).

"Plasma per cent means the percentage of the whole blood which the plasma constitutes, and is obtained by dividing the total number of cubic centimeters of oxalated plasma present in the hematocrit tube minus 2, by the total contents of the tube in cubic centimeters minus 2.

"Then:

$$\text{"The plasma volume (in c.c.)} = \frac{26666.67 D C}{R}$$

$$\text{"The blood volume} = \frac{\text{Plasma volume} \times 100}{\text{Plasma per cent}}$$

"The above formula for plasma volume may be derived as follows: The standard for color comparison contains 0.75 c.c. of 1 per cent dye in 200 c.c. of fluid, or 1 c.c. in $266.66 +$ c.c. D c.c. of 1 per cent dye (the amount injected) will impart the same color intensity to $266.6667 D$ c.c. of fluid. If, however, the color intensity is $\frac{R}{100 C}$ (that is the colorimetric reading in per cent corrected for the dilution of the plasma by the oxalate solution), the number of cubic centimeters of fluids equals $\frac{(266.6667 D) (100 C)}{R}$ or $\frac{26666.67 D C}{R}$."

SOME TECHNICAL CONSIDERATIONS IN THE DETERMINATION OF BLOOD VOLUME

In our work all determinations have been made on patients under basal conditions. That is to say, all determinations have been carried out in the morning at practically the same time; the subjects have had no breakfast and have been kept in a supine position. The ambulatory patients were kept in a supine position for at least twenty to thirty minutes before the test was started.

After the test was completed, the arm was examined as a routine for any trace of dye in subcutaneous tissue. In those cases in which evidence of the dye appeared outside of the veins the determination was discarded, or repeated after a suitable lapse of time.

As a rule, the needles used were of 19 gauge. The bevels were short to avoid any leakage of dye from the vein. Record syringes with Luer attachments were used because of their accuracy, and the syringes were recalibrated. In most instances, however, the original calibrations were correct.

After the blood had been transferred into the centrifuge tubes, they immediately were capped with heavy finger cots

which, to avoid evaporation, were left on during the time of centrifugalization.

REPEATED DETERMINATIONS OF BLOOD VOLUME AT SHORT INTERVALS

Repeated determinations of blood volume at short intervals by means of the dye method are possible and have been investigated by Smith⁹⁵ and in our laboratory.¹¹¹ The method, as used in our laboratory, is particularly feasible for use in the experimental animal, and it involves a minimal calculation.

When a second determination of blood volume is attempted after a short interval the plasma remains colored from the previous determination, and this coloring must be taken into account in both the standard and the unknown samples. In order to determine the blood volume the second time 10 c.c. of blood is withdrawn for the standard. Then the second injection of dye is made and blood withdrawn three minutes afterward. All four tubes are centrifugalized and the hematocrit readings are taken as before.

The standard is prepared by mixing 2 c.c. of plasma obtained before the second injection, 2 c.c. of 1 : 200 dilution of the dye injected, and 4 c.c. of physiologic sodium chloride solution. The unknown is prepared by mixing 2 c.c. of plasma obtained from blood drawn following the second injection, and 6 c.c. of physiologic solution of sodium chloride.

The colorimeter is set at 10 and the unknown is compared with the standard. The calculation is the same as that carried out in the single determination.

The question of untoward results following the reinjection of the dye has been considered. In the experimental animal untoward effects were not noted. Visible staining of tissue was not observed. In the human subject the increased concentration of the dye in the plasma was visible through the skin of a

TABLE 5

REPEATED DETERMINATIONS AT SHORT INTERVALS ON NORMAL DOGS

Dog.	Date.	Weight, kg.	Time of day.	Cells by hema- tOCRIT, per cent.	Plasma volume, c.c.		Blood volume, c.c.	
					Total.	For each kg. of body weight.	Total.	For each kg. of body weight.
1	2/20/28	6.2	10.00 a.m.	35	370	59.7	570	92.1
			10.30 a.m.	35	377	60.8	580	93.5
	2/27/28	6.47	9.00 a.m.	32	441	68.3	650	100.4
			9.30 a.m.	32	435	67.3	640	99.0
			12.30 p.m.	32	425	65.8	625	96.8
2	2/20/28	19.05	9.00 a.m.	42	882	46.0	1,520	80.0
			11.00 a.m.	42	882	46.2	1,520	80.0
	2/21/28	19.00	8.00 a.m.	42	853	44.8	1,470	77.5
			11.45 a.m.	42	853	44.8	1,470	77.5
			1.15 p.m.	42	853	44.8	1,470	77.5
3	2/23/28	11.15	9.00 a.m.	37	740	66.4	1,174	105.2
			9.20 a.m.	37	740	66.4	1,174	105.2
			12.30 p.m.	37	744	66.7	1,180	105.8

blond subject for several hours. This disappeared with the removal of the dye from the blood stream. Tissue was not stained. The concentration of the dye in the blood is less than that which is necessary to cause adsorption of dye by the erythrocytes, as has been shown by experiments in vitro (page 26 et seq.).

More extensive study of repeated determinations in the human subject has been omitted because of the risk of dis-

coloration of the arm by leakage of the dye into the tissues, because of general discoloration due to the great concentration of the dye, and because of the possibility of toxic effects after repeated determinations.

Results of repeated determinations of blood volume at short intervals in five experiments on three animals are shown in Table 5.

Chapter IV

SUMMARY OF MATTER RELATING TO THE METHOD

In the foregoing pages we have attempted to consider all the criticisms which have been made against the dye method of determining blood volume and plasma volume and have discussed the various constructive suggestions that have been offered concerning changes in technic. The results of control studies are presented together with such conclusions as seem justified.

Choice of dye.—Vital red is, in our opinion, entirely satisfactory for determinations of blood volume. On the other hand, vital red is not generally available since it is not used commercially. Hence a substitute is desirable. Congo-red, as suggested by Harris, has proved equally satisfactory. As stated in our original paper,⁶⁴ "It is probable that many dyes will answer the purpose equally well."*

Condition of patient for test.—Our determinations throughout concern basal blood volumes from determinations made in the morning, following sleep, and with the patient at rest. If it is true, as has been suggested, that blood volume is affected by exercise, then we are faced by a new problem, the quantitative effects of exercise on blood volume. However, Whipple,⁶⁸ in his study of the effects of vigorous exercise in dogs, found that no maintained or constant effects on plasma volume could be demonstrated. The opinion of Lindhard⁷² that blood volume

* Congo-red used in certain conditions (amyloid disease) disappears more rapidly from the blood. This condition did not enter into our cases. Nevertheless, such possibilities should be kept in mind with any dye or colloid.

values are acceptable only during and immediately after exercise is not borne out by the studies herein reported.

Interval between injection of dye and collection of blood.—The determination of blood volume should be made from three to six minutes after the injection of the dye.

Distribution of erythrocytes; vessels employed in test.—Uneven distribution of erythrocytes in plasma in different vessels has not been proved to be a serious source of error in the method. In our routine work, the dye was introduced into a vein of one arm and collected from a vein of the other.

Dependability of hematocrit values.—The hematocrit determinations as obtained in this method are not subject to great inaccuracy.

Use of wet oxalate method.—Whipple's⁵⁹ criticism of our technic relative to the shrinkage of erythrocytes resulting from the employment of dry oxalate as an anticoagulant is sound. Consequently, we have accepted Whipple's criticism and are now using the oxalate solution as an anticoagulant.

Safety.—The dye method is entirely safe.

Combined methods.—We do not favor the suggestion of utilizing a combination of the method for plasma volume and the carbon monoxide method for the determination of true blood volume. We find the dye method in itself sufficient for our clinical needs. A study of the literature reveals several features which we would consider as disadvantages to the carbon monoxide method.

Chapter V

NORMAL SUBJECTS*

The normal values here presented are based on a study of forty-nine men and twenty-five women. These included physicians, laboratory workers, and patients in the clinic who, after careful examination, appeared to be normal. Unusually thin or stout persons were excluded. The ages varied from seventeen to sixty-three years, with the mean about thirty-five. The protocols are given in Tables 6 and 7 on pages 55, 56 and 57.

BLOOD VOLUME OF ADULTS GROUPED ACCORDING TO BODY BUILD

As normal persons are subject to wide variations in build, the two groups of men and women have been divided each into three subgroups: Underweight, standard, and overweight. The standard subjects were those whose weight, taking into consideration sex, height, and age, varied less than 10 per cent from the actuarial figures commonly in use. The underweight and overweight persons varied more than 10 per cent from these standards, but still not enough to warrant their being called abnormal or diseased.

From the means given in Table 8 and plotted in Figure 1 it will be seen that as one passes from the underweight to the standard and overweight groups there is a small but definite

* The mean values and the range for normal persons, as collected from Tables 6, 7, 8, and 9, are given in Table 47, just preceding the Index. This material is so placed in the book to make the table available for ready reference.

TABLE 6

BLOOD VOLUME AND PLASMA VOLUME IN FORTY-NINE NORMAL MEN OF VARYING BODY BUILD

Case.	Weight, kg.	Height, cm.	Body surface, sq. m.	Age, years.	Cells by hematocrit, per cent.	Blood.			Plasma.			Hemoglobin.			
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total gm.	Gm. in each 100 c.c. of blood.	Gm. for each kg. of body weight.	Gm. for each sq. m. of body surface.
Underweight															
1	62	175	1.75	25	40	6,250	101	3,570	3,750	60	2,140	1,163	18.6	11.8	664
2	60	167	1.68	38	38	5,320	88	3,170	3,300	54	1,960	835	15.7	13.9	497
3	51	163	1.54	19	40	4,940	96	3,200	2,960	58	1,920	776	15.7	15.2	504
4	57	165	1.60	36	43	5,520	97	3,450	3,150	55	1,970	960	17.4	17.2	600
5	60	167	1.68	36	41	5,400	90	3,210	3,180	53	1,895	864	16.0	14.4	514
6	65	175	1.80	31	42	5,980	92	3,370	3,490	54	1,930	1,047	17.5	16.1	581
7	70	175	1.85	62	47	5,900	84	3,190	3,130	44	1,690	1,056	17.9	15.1	571
8	60	172	1.73	36	41	5,130	85	2,970	3,020	50	1,750	831	16.2	13.9	483
9	53	156	1.53	58	40	5,000	94	3,260	3,000	57	1,960	790	15.8	14.9	576
10	61	174	1.71	28	43	5,440	89	3,180	3,100	50	1,810	893	16.4	14.6	522
11	60	174	1.70	27	45	5,360	89	3,150	2,950	49	1,735	917	17.1	15.3	539
12	57	167	1.63	27	41	5,650	99	3,465	3,330	58	2,040	893	15.8	15.6	548
Standard weight															
1	75	167	1.85	44	40	5,770	77	3,120	3,460	46	1,870	912	15.8	12.0	493
2	62	170	1.74	24	38	6,020	97	3,460	3,740	60	2,150	945	15.7	15.2	543
3	70	170	1.80	25	45	6,480	92	3,600	3,560	50	1,975	1,179	18.2	16.8	656
4	68	165	1.75	42	42	4,770	70	2,730	2,770	40	1,580	785	16.5	11.6	448
5	72	172	1.88	43	43	5,900	82	3,130	3,360	46	1,790	938	15.9	13.0	498
6	68	172	1.82	22	41	6,100	90	3,350	3,600	53	1,980	926	15.2	13.6	309
7	70	172	1.84	25	45	7,360	105	4,000	4,050	58	2,200	1,170	15.9	16.7	630
8	80	180	2.00	24	44	7,140	89	3,570	4,000	50	2,000	1,100	15.4	13.7	550
9	69	171	1.82	33	41	5,810	84	3,180	3,430	50	1,880	1,074	18.5	15.3	587
10	58	165	1.55	24	45	5,540	96	3,570	3,050	53	1,965	1,147	20.7	19.8	740
11	68	172	1.83	29	40	6,660	98	3,640	4,000	59	2,180	1,052	15.9	15.5	575
12	60	162	1.64	28	42	5,930	99	3,610	3,440	57	2,100	936	15.8	15.6	571

TABLE 6—Continued

BLOOD VOLUME AND PLASMA VOLUME IN FORTY-NINE NORMAL MEN OF VARYING BODY BUILD

Case.	Weight, kg.	Height, cm.	Body surface, sq. m.	Age, years.	Cells by hematocrit, per cent.	Blood.			Plasma.			Hemoglobin.			
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total gm.	Gm. in each 100 c.c. of blood.	Gm. for each kg. of body weight.	Gm. for each sq. m. of body surface.
Standard weight															
13	58	164	1.62	28	44	4,640	80	2,865	2,600	44	1,600	794	17.1	13.7	490
14	73	178	1.89	36	42	6,530	90	3,460	3,790	52	2,000	1,064	16.3	15.6	563
15	74	170	1.86	25	39	6,151	83	3,330	3,750	51	2,010	1,058	17.2	14.3	622
16	74	164	1.80	43	43	6,280	86	3,530	3,640	49	2,040	1,160	17.9	15.4	644
17	70	178	1.86	29	44	6,240	89	3,350	3,500	47	1,875	1,160	18.6	16.5	624
18	85	180	2.05	36	42	6,970	82	3,395	4,040	47	1,970	1,108	15.9	13.0	535
19	64	163	1.70	44	41	6,040	95	3,550	3,560	55	2,090	1,075	17.8	16.8	632
20	67	168	1.78	35	40	6,390	96	3,580	3,830	57	2,160	993	15.4	14.8	561
21	71	168	1.81	29	43	6,070	85	3,350	3,460	48	1,920	1,062	17.5	15.0	589
22	64	169	1.75	44	46	5,550	86	3,170	3,000	46	1,720	747	14.8	11.8	427
23	79	183	2.00	30	47	8,080	102	4,040	4,280	54	2,140	1,616	20.0	20.2	808
24	65	172	1.79	35	42	5,860	90	3,273	3,400	52	1,890	1,061	18.1	16.3	593
25	74	177	1.92	41	40	7,130	96	3,710	4,280	57	2,230	1,123	15.8	15.2	576
26	67	175	1.82	30	45	7,190	107	3,953	3,955	60	2,170	1,220	17.0	18.8	670
27	74	180	1.94	29	44	6,060	82	3,126	3,400	45	1,750	1,074	17.7	14.5	554
28	59	168	1.65	30	40	4,880	82	2,960	2,925	49	1,772	712	14.6	12.0	432
29	77	175	1.92	33	42	5,910	77	3,410	3,430	44	1,785	998	16.9	12.9	520
Overweight															
1	71	165	1.77	26	42	5,350	75	3,020	3,100	43	1,750	872	16.3	12.0	493
2	68	177	1.85	52	36	5,920	87	3,200	3,790	55	2,050	858	14.5	12.6	464
3	73	168	1.85	17	42	5,750	79	3,110	3,330	45	1,800	920	16.0	12.6	497
4	87	172	2.00	30	47	7,000	80	3,500	3,710	42	1,850	1,134	16.2	13.0	567
5	75	166	1.84	26	40	6,940	93	3,770	4,160	56	2,260	1,186	17.1	15.8	647
6	85	169	1.96	49	42	5,590	66	2,850	3,240	38	1,655	988	17.7	11.6	504
7	77	173	1.90	31	47	6,800	88	3,580	3,600	46	1,890	1,074	15.8	14.0	565
8	85	170	1.96	57	43	7,330	86	3,750	4,180	49	2,130				

TABLE 7

BLOOD AND PLASMA VOLUME IN TWENTY-FIVE NORMAL WOMEN OF VARYING BODY BUILD

Case.	Weight, kg.	Height, cm.	Body surface, sq. m.	Age, years.	Cells by hematocrit, per cent.	Blood.			Plasma.			Hemoglobin.			
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total gm.	Gm. in each 100 c.c. of blood.	Gm. for each kg. of body weight.	Gm. for each sq. m. of body surface.
Underweight															
1	53	165	1.56	24	38	5,525	104	3,540	3,430	65	2,200	779	14.1	14.7	449
2	55	159	1.55	53	38	4,880	88	3,120	3,025	55	1,940	615	12.6	11.2	397
3	54	160	1.54	63	40	4,445	82	2,890	2,665	49	1,730	565	12.7	10.4	368
4	50	165	1.53	47	37	5,395	106	3,510	3,395	68	2,220	755	14.0	15.1	493
5	52	164	1.54	23	42	5,165	99	3,355	3,000	57	1,950	790	15.3	15.2	513
6	58	169	1.66	42	35	5,650	97	3,390	3,675	63	2,215	798	12.4	13.7	481
7	55	163	1.58	41	42	4,395	80	2,780	2,550	46	1,615	730	16.6	13.2	462
8	55	157	1.54	60	40	4,135	75	2,685	2,480	45	1,600	608	14.7	11.0	394
Standard weight															
1	70	162	1.75	56	42	5,025	72	2,890	2,925	42	1,670	754	15.0	11.1	434
2	57	158	1.58	39	36	5,350	94	3,385	3,425	60	2,165	679	12.7	11.9	430
3	65	166	1.71	25	41	5,440	83	3,180	3,210	49	1,875	849	15.6	13.0	497
4	65	170	1.74	42	48	5,165	80	2,970	2,950	45	1,695	806	15.6	12.4	460
5	52	154	1.48	25	43	4,355	84	2,950	2,485	47	1,690	563	15.0	10.8	380
6	64	167	1.72	25	42	5,640	88	3,275	3,270	51	1,960	773	13.7	12.0	452
7	62	163	1.68	24	39	4,800	77	2,855	2,925	47	1,740	667	13.9	10.7	397
8	62	163	1.68	24	37	5,400	87	3,210	3,400	55	2,025	697	12.9	11.2	414
9	56	157	1.55	35	42	5,390	96	3,485	3,130	55	2,015	841	15.6	15.0	543
10	56	164	1.60	23	40	4,375	78	2,730	2,625	47	1,640	634	14.5	11.3	396
11	56	160	1.57	22	38	4,880	87	3,100	3,025	54	1,925	688	14.1	12.3	438
12	53	158	1.52	27	36	4,550	85	2,880	2,910	54	1,840	632	13.1	11.9	416
Overweight															
1	63	164	1.66	17	40	5,210	83	3,130	3,130	49	1,885	686	13.2	10.9	413
2	64	160	1.66	22	41	6,125	97	3,690	3,615	57	2,175	956	15.6	15.2	576
3	68	164	1.73	35	40	5,200	76	3,000	3,125	46	1,800	728	14.0	10.7	421
4	70	163	1.75	37	41	5,125	73	2,940	3,025	43	1,725	764	14.9	10.9	437
5	73	157	1.73	58	38	5,220	72	3,015	3,240	44	1,875	677	13.0	9.2	391

TABLE 8

MEAN VALUES IN NORMAL SUBJECTS OF DIFFERENT BODY BUILDS

	Cases.	Sex.	Weight, kg.	Height, cm.	Body surface, sq. m.	Blood.		Plasma.		Hemoglobin.			Cells by hematocrit, per cent.
						C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Gm. in each 100 c.c. of blood.	Gm. for each kg. of body weight.	Gm. for each sq. m. of body surface.	
Underweight ...	12	M.	59.6	169.0	1.68	92.0	3,265	53.5	1,900	16.8	14.9	547	41
Standard.....	29	M.	69.5	171.2	1.82	89.1	3,410	51.0	1,958	16.7	15.0	541	42
Overweight.....	8	M.	77.6	170.0	1.89	81.8	3,347	46.7	1,923	16.3	13.3	532	42
Underweight ...	8	F.	54.0	163.0	1.56	91.3	3,180	56.0	1,933	14.1	13.1	451	39
Standard.....	12	F.	59.3	162.0	1.63	84.2	3,075	50.5	1,848	14.4	12.0	437	40
Overweight.....	5	F.	67.6	161.0	1.70	80.2	3,155	47.8	1,892	14.2	11.1	444	40
All groups.....	49	M.	68.1	170.0	1.80	88.6	3,365	51.0	1,938	16.4	14.7	541	42
All groups.....	25	F.	59.7	162.0	1.60	85.7	3,130	51.7	1,885	14.2	12.2	442	40
Total.....	74		65.9	167.9	1.7	87.7	3,278	51.2	1,920	15.7	13.8	508	41
Mean values for men expressed as percentages of values for women.....						103.3	107.3	98.7	102.8				105.0
Mean values for "normal" men expressed as percentages of values for "normal" women						105.7	110.8	100.9	105.9				105.0

decrease in the amount of blood in the body for each kilogram of body weight. The mean blood volume for each kilogram for the underweight men was 92 c.c., for the standard men, 89.1 c.c.; for the overweight men, 81.8 c.c., and for all together 88.6 c.c. There was in the three weight groups less variation in the mean amount of blood for each square meter of body surface than in the amount for each kilogram which, as will be brought out later, is an important point. In standard men, the mean amount of blood for each square meter of body surface was 3,410 c.c. The mean plasma volume for each kilogram of body weight varied in the three weight groups of men much as did the blood volume. For all men taken together the

mean plasma volume for each kilogram of body weight was 51 c.c., and for each square meter of body surface it was 1,938 c.c.

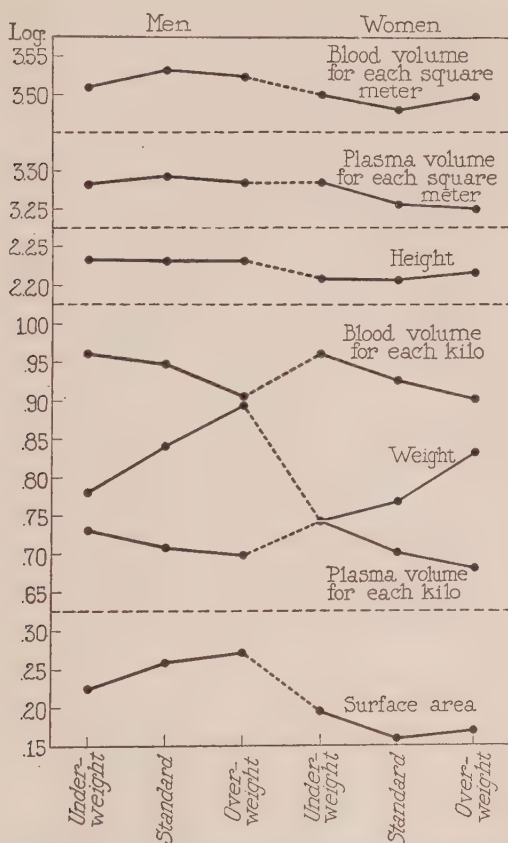


FIG. 1.—Mean blood volume and plasma volume, according to body weight and body surface, expressed logarithmically for normal individuals of different weight groups.

The mean blood volume in the three weight groups of women varied much as it did in the corresponding groups of men. The underweight women were found to have 91.3 c.c. of blood for

each kilogram of body weight; the standard women, 84.2 c.c.; the overweight women, 80.2 c.c., and all together, 85.7 c.c. Just as in men, the variation in blood volume and plasma

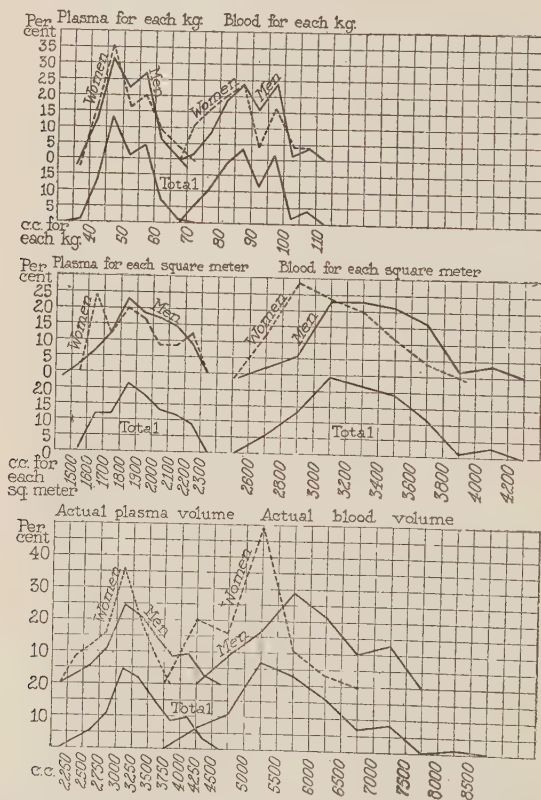


FIG. 2.—Percentage distribution of plasma volume and blood volume for normal men and normal women.

volume in the three groups was less marked when the figures were expressed in terms of body surface than when they were expressed in terms of body weight. Although women, with their smaller bodies, have on the average considerably less

blood and plasma than men, the amounts for each kilogram of weight and each square meter of body surface are almost the same.

Taking all the men and all the women together, the mean amount of blood for each kilogram of body weight was 87.7 c.c., and the mean amount for each square meter of body surface was 3,278 c.c. The corresponding figures for plasma volume were 51.2 c.c. and 1,920 c.c. Table 8 gives the mean values for all the groups, and Figure 2 shows the percentage distributions of plasma volume and blood volume for normal men and women.

As will be seen from Table 9, the men had 19 per cent more blood than the women, but only 13 per cent more plasma. Obviously, then, their cell volume was 6 per cent larger than that of the women. The amount of plasma for each kilogram of weight and each square meter of body surface was about the same for men and women, but the blood volume for each square meter was 7.5 per cent greater in men than in women. These figures, however, will certainly be changed somewhat as more measurements are studied and they will always depend somewhat on the number of underweight and overweight persons included.

Incidentally it was noted that women have a smaller amount of circulating hemoglobin in proportion to body weight and body surface than have men. The figures (Table 8) were, for the women, 12.2 gm. for each kilogram and 442 gm. for each square meter of body surface, and for the men, 14.7 gm. for each kilogram and 541 gm. for each square meter of body surface. The mean for the two sexes was 13.8 gm. for each kilogram and 508 gm. for each square meter. There is also, in the different groups of subjects, more constant relation between hemoglobin values and body surface than between hemoglobin values and body weight.

TABLE 9
MEANS, STANDARD DEVIATIONS, AND PROBABLE ERROR OF THE VARIOUS
DISTRIBUTIONS

		Men and women, 74 cases.	Men, 49 cases.	Women, 25 cases.
Height.	Mean.....	167.9 cm.	170.0 cm.	162.1 cm.
	Standard deviation....	7.00 cm.	5.66 cm.	3.93 cm.
Weight.	Mean.....	65.9 kg.	68.1 kg.	59.7 kg.
	Standard deviation....	8.75 kg.	8.11 kg.	6.48 kg.
Surface area.	Mean.....	1.74 sq. m.	1.8 sq. m.	1.62 sq. m.
	Standard deviation....	0.14 sq. m.	0.12 sq. m.	0.08 sq. m.
Index of fullness.	Mean.....	139.0	138.3	140.2
	Standard deviation....	17.7	15.6	16.8
Age.	Mean.....	34.8 yrs.	33.7 yrs.	35.5 yrs.
	Standard deviation....	11.4 yrs.	9.6 yrs.	13.8 yrs.
Blood volume.	Mean.....	5,710 c.c.	6,040 c.c.	5,076 c.c.
	Standard deviation....	839 c.c.	758 c.c.	480 c.c.
Plasma volume.	Mean.....	3,350 c.c.	3,475 c.c.	3,075 c.c.
	Standard deviation....	458 c.c.	403 c.c.	325 c.c.
Blood volume for each kg. of body weight.	Mean.....	87.7 c.c.	88.6 c.c.	85.7 c.c.
	Standard deviation....	8.5 c.c.		
	Probable error of mean.	± 0.7 c.c.		
Blood volume for each sq. m. of body surface.	Mean.....	3,278 c.c.	3,365 c.c.	3,130 c.c.
	Standard deviation....	307 c.c.		
	Probable error of mean.	± 25 c.c.		
Plasma volume for each kg. of body weight.	Mean.....	51.2 c.c.	51.0 c.c.	51.7 c.c.
	Standard deviation....	6.3 c.c.		
	Probable error of mean.	± 0.5 c.c.		
Plasma volume for each sq. m. of body surface.	Mean.....	1,920 c.c.	1,938 c.c.	1,885 c.c.
	Standard deviation....	185 c.c.		
	Probable error of mean.	± 15 c.c.		

Correlation of blood volume and plasma volume with various body measurements.—In order to determine whether it would be possible to predict blood volume or plasma volume in a given man or woman, we first studied the correlations between the blood volume and plasma volume on the one side, and the various body measurements such as height, weight, and body surface on

the other. Figure 3 shows some of the necessary double entry tables with which such a study begins. If all the data were to fall on a diagonal across one of these charts, correlation would, of course, be perfect and the coefficient would be ± 1.0 . Figure 3 shows there is a higher degree of correlation, or less

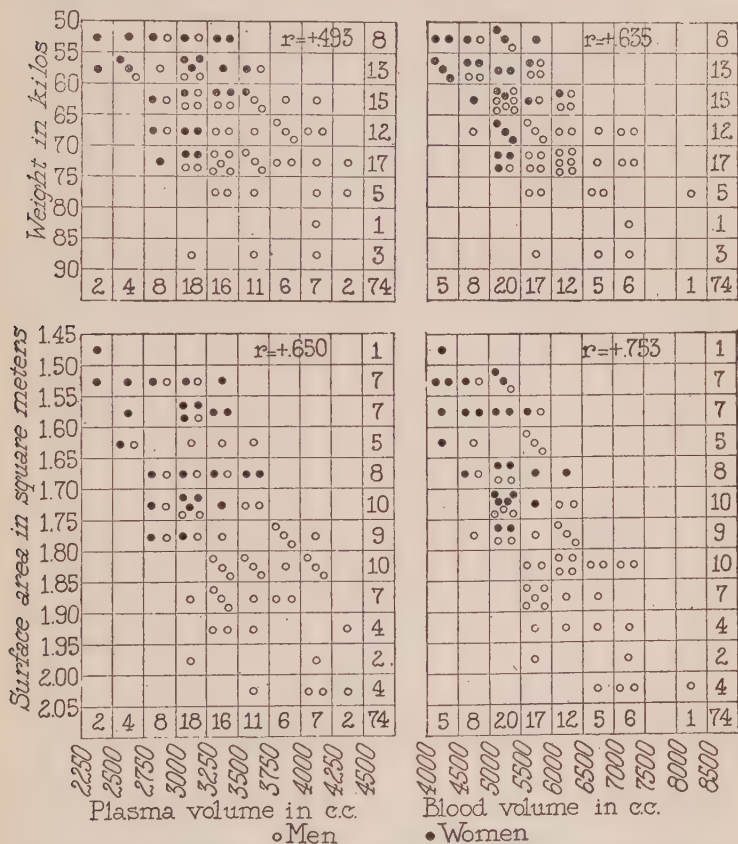


FIG. 3.—The correlation between blood volume and plasma volume and body weight and body surface.

scatter from the diagonal, between blood volume and plasma volume and body surface than between blood volume and plasma volume and weight. A fair degree of correlation was found between blood volume and height. The various coefficients are given in Table 10, in which it will be seen that those for plasma

TABLE 10
COEFFICIENTS OF CORRELATION AND REGRESSION FORMULAS *

	Totals.	Men.	Women.
Blood volume to surface area.....	$+ 0.753 \pm 0.04$	0.698 ± 0.05	$+ 0.439 \pm 0.10$
Blood volume to surface area (age constant).....	$+ 0.763$		
Blood volume to surface area (age and fullness index constant).....	$+ 0.815$		
Blood volume to height.....	$+ 0.635 \pm 0.05$	$+ 0.474 \pm 0.08$	$+ 0.413 \pm 0.10$
Blood volume to weight.....	$+ 0.635 \pm 0.05$	$+ 0.619 \pm 0.06$	$+ 0.356 \pm 0.12$
Blood volume to age.....	$- 0.131 \pm 0.08$	$- 0.152 \pm 0.09$	$- 0.250 \pm 0.12$
Blood volume to age (surface area constant).....	$- 0.239$		
Blood volume to age (for each sq. m.)	$- 0.262 \pm 0.07$		
Blood volume to fullness index (for each sq. m.).....	$- 0.124 \pm 0.08$		
Blood volume to height (weight constant).....	$+ 0.407$		
Blood volume to weight (height constant).....	$+ 0.403$		
Plasma volume to surface area.....	$+ 0.650 \pm 0.05$	$+ 0.644 \pm 0.05$	$+ 0.335 \pm 0.12$
Plasma volume to height.....	$+ 0.445 \pm 0.06$	$+ 0.439 \pm 0.08$	$+ 0.364 \pm 0.12$
Plasma volume to weight.....	$+ 0.493 \pm 0.06$	$+ 0.506 \pm 0.07$	$+ 0.236 \pm 0.12$
Plasma volume to age.....	$- 0.105 \pm 0.08$	$- 0.037 \pm 0.09$	$- 0.250 \pm 0.12$
Plasma volume to age (for each sq. m.).....	$- 0.166 \pm 0.08$		
Weight to height.....	$+ 0.611 \pm 0.05$		
Weight to surface area.....	$+ 0.792 \pm 0.03$		

* Blood volume = $4,480 \times \text{surface area} - 2,110$ or $4,530 \times \text{surface area} - 11.5 \times \text{age} - 8.1 \times \text{fullness index} - 600$. Plasma volume = $2,110 \times \text{surface area} - 310$.

volume were all lower than the corresponding ones for blood volume. Furthermore, all were lower in women than in men. This is due partly perhaps to the greater amount of body fat in women (fat having a poor blood supply) and partly to the smallness of the groups studied. Whatever the reason, until more measurements are made and better coefficients computed it will be more difficult to predict blood volume in women than in men.

From the correlation coefficients and standard deviations we derived the usual formulas for regression lines, and from the one representing the relation between blood volume and body surface, we found we could predict the blood volume of well proportioned men with an error of ± 3.3 per cent (Table 11).

**TABLE 11.—BLOOD VOLUME IN CUBIC CENTIMETERS CALCULATED FROM
THE SURFACE AREA IN SQUARE METERS ***

Surface area.	Blood volume.	Surface area.	Blood volume.	Surface area.	Blood volume.	Surface area.	Blood volume.	Surface area.	Blood volume.
1.25	3,490	1.50	4,610	1.75	5,730	2.00	6,850	2.25	7,970
1.26	3,535	1.51	4,655	1.76	5,775	2.01	6,895	2.26	8,015
1.27	3,580	1.52	4,700	1.77	5,820	2.02	6,940	2.27	8,060
1.28	3,624	1.53	4,744	1.78	5,864	2.03	6,984	2.28	8,104
1.29	3,669	1.54	4,789	1.79	5,909	2.04	7,029	2.29	8,149
1.30	3,714	1.55	4,834	1.80	5,954	2.05	7,074	2.30	8,194
1.31	3,759	1.56	4,879	1.81	5,999	2.06	7,119	2.31	8,239
1.32	3,804	1.57	4,924	1.82	6,044	2.07	7,164	2.32	8,284
1.33	3,848	1.58	4,968	1.83	6,088	2.08	7,208	2.33	8,328
1.34	3,893	1.59	5,013	1.84	6,133	2.09	7,253	2.34	8,373
1.35	3,938	1.60	5,058	1.85	6,178	2.10	7,298	2.35	8,418
1.36	3,983	1.61	5,103	1.86	6,223	2.11	7,343	2.36	8,463
1.37	4,028	1.62	5,148	1.87	6,268	2.12	7,388	2.37	8,508
1.38	4,072	1.63	5,192	1.88	6,312	2.13	7,432	2.38	8,552
1.39	4,117	1.64	5,237	1.89	6,357	2.14	7,477	2.39	8,597
1.40	4,162	1.65	5,282	1.90	6,402	2.15	7,522	2.40	8,642
1.41	4,207	1.66	5,327	1.91	6,447	2.16	7,567	2.41	8,687
1.42	4,252	1.67	5,372	1.92	6,492	2.17	7,612	2.42	8,732
1.43	4,296	1.68	5,416	1.93	6,536	2.18	7,656	2.43	8,776
1.44	4,341	1.69	5,461	1.94	6,581	2.19	7,701	2.44	8,821
1.45	4,386	1.70	5,506	1.95	6,626	2.20	7,746	2.45	8,866
1.46	4,431	1.71	5,551	1.96	6,671	2.21	7,791	2.46	8,911
1.47	4,476	1.72	5,596	1.97	6,716	2.22	7,836	2.47	8,956
1.48	4,520	1.73	5,640	1.98	6,760	2.23	7,880	2.48	9,000
1.49	4,565	1.74	5,685	1.99	6,805	2.24	7,925	2.49	9,045

* The figures are based on a short formula (page 66) which does not take into account any correction for age or body build.

The usefulness of body surface as an index to blood volume was to be expected from the fact that it is a function

$$(\text{Area in sq. cm.} = \text{Wt. in kg. } 0.425 \times \text{Ht. in cm. } 0.725 \times 71.84)$$

of height and weight, both of which are well correlated with blood volume. Height and weight are also well correlated one with the other, which explains the fact, shown by a study of partial correlations, that if one is held constant, the relation between the other and blood volumes becomes less marked (Table 10). In other words, the high correlations between, let us say, height and blood volume are due partly to the correlation with weight which commonly varies in the same direction as height.

So far as we know, Dreyer and Ray were the first to note (in small mammals) that blood volume is correlated better with body surface than with weight. There is, however, some question in our minds how closely their formula represents body surface since we have been unable to find where they have discussed that phase of the matter. It should be noted also that their

formula, $B = \frac{W^{2/3}}{k}$ (in which B represents blood volume in cubic centimeters,

W , weight in grams, and k , a constant varying with different species of animals) is that of a curve whereas all of our tests on the correlations between blood volume and weight and body surface indicate that within the range of our data we are dealing with straight lines.

To estimate the blood volume of a normal person with average build and age between thirty and forty, the first thing to do is to find the body surface corresponding to the subject's weight and height. This can be done with the help of the Boothby-Sandiford nomogram (Fig. 4) computed from the Du Bois standards for body surface. Then the blood volume may be read in Table 11. With a person of unusual build or with age widely divergent from thirty-five years, the mean of our groups of normals, it will probably be better to use another and slightly more complex formula.

It has already been pointed out that the blood volume for each unit of body weight varies inversely as the amount of fat present in the body. In order to express this relation numerically so as to plot it in a correlation table we had to get some index of fatness, and following the advice given by Martin in his "*Lehrbuch der Anthropologie*," we adopted Rohrer's *index of body fullness*. As he pointed out, body size varies in three dimensions while height varies in only one, so one must divide the weight in kilograms by the cube of the height in centimeters. (Unfortunately the results obtained are affected not only by the amount of fat present but also by the relative length of trunk and legs.) We have used as denominator the first three figures of the cubic product and in the quotient again we have kept three figures. As was to be expected, we found a slight degree of negative correlation between the fullness index and the blood volume for each square meter of body surface. The coefficient was -0.124 ± 0.08 .

CHART FOR BASAL METABOLIC RATE DETERMINATIONS

WM. BOOTHBY. R. SANDIFORD.
SEPTEMBER 1920.

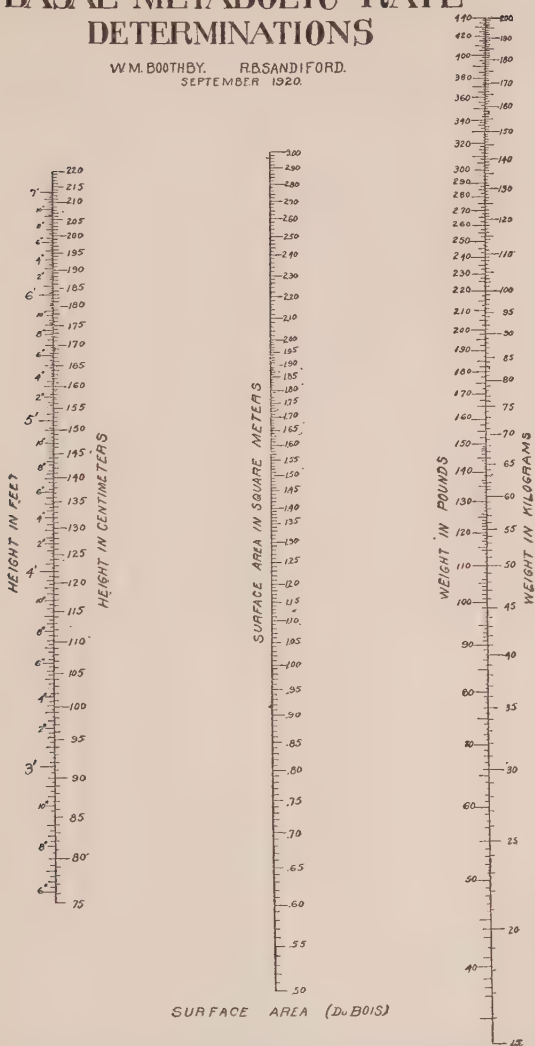


FIG. 4.—Boothby-Sandiford nomographic chart for obtaining body surface according to the Du Bois standard.

It is obvious also that human beings tend to shrivel and dry up as they grow old, so we were not surprised to find a small negative correlation between age and blood volume for each square meter. The coefficient was -0.262 ± 0.07 .

TABLE 12

FOR COMPUTATION OF BLOOD VOLUME IN THIN AND FAT AND IN YOUNG AND OLD PERSONS *

Surface area, sq. m.		Surface area, sq. m.		Surface area, sq. m.		Surface area, sq. m.		Surface area, sq. m.	
1.25	5,063	1.50	6,195	1.75	7,328	2.00	8,460	2.25	9,593
1.26	5,108	1.51	6,240	1.76	7,373	2.01	8,505	2.26	9,638
1.27	5,153	1.52	6,286	1.77	7,418	2.02	8,551	2.27	9,683
1.28	5,198	1.53	6,331	1.78	7,463	2.03	8,596	2.28	9,728
1.29	5,244	1.54	6,376	1.79	7,509	2.04	8,641	2.29	9,774
1.30	5,289	1.55	6,422	1.80	7,554	2.05	8,687	2.30	9,819
1.31	5,334	1.56	6,467	1.81	7,599	2.06	8,732	2.31	9,864
1.32	5,380	1.57	6,512	1.82	7,645	2.07	8,777	2.32	9,910
1.33	5,425	1.58	6,557	1.83	7,690	2.08	8,822	2.33	9,955
1.34	5,470	1.59	6,603	1.84	7,735	2.09	8,868	2.34	10,000
1.35	5,516	1.60	6,648	1.85	7,781	2.10	8,913	2.35	10,046
1.36	5,561	1.61	6,693	1.86	7,826	2.11	8,958	2.36	10,091
1.37	5,606	1.62	6,739	1.87	7,871	2.12	9,004	2.37	10,136
1.38	5,651	1.63	6,784	1.88	7,916	2.13	9,049	2.38	10,181
1.39	5,697	1.64	6,829	1.89	7,962	2.14	9,094	2.39	10,227
1.40	5,742	1.65	6,875	1.90	8,007	2.15	9,140	2.40	10,272
1.41	5,787	1.66	6,920	1.91	8,052	2.16	9,185	2.41	10,317
1.42	5,833	1.67	6,965	1.92	8,098	2.17	9,230	2.42	10,363
1.43	5,878	1.68	7,010	1.93	8,143	2.18	9,275	2.43	10,408
1.44	5,923	1.69	7,056	1.94	8,188	2.19	9,321	2.44	10,453
1.45	5,969	1.70	7,101	1.95	8,234	2.20	9,366	2.45	10,499
1.46	6,014	1.71	7,146	1.96	8,279	2.21	9,411	2.46	10,544
1.47	6,059	1.72	7,192	1.97	8,324	2.22	9,457	2.47	10,589
1.48	6,104	1.73	7,237	1.98	8,369	2.23	9,502	2.48	10,634
1.49	6,150	1.74	7,282	1.99	8,415	2.24	9,547	2.49	10,680

* Figures to be used in the computation of blood volume according to the formula:

$$Bv = 4.530 \times Sa - 11.5 \times Age - 8.1 \times Fi - 600$$

where Bv = blood volume, Sa = surface area, and Fi = fullness index. This formula should be used when the subject is old or young or abnormally thin or stout.

TABLE 12—Continued

FOR COMPUTATION OF BLOOD VOLUME IN THIN AND FAT AND IN YOUNG AND OLD PERSONS*

Age.		Age.		Fullness index.		Fullness index.		Fullness index.	
15	173	45	518	110	891	140	1,184	170	1,377
16	184	46	529	111	899	141	1,142	171	1,385
17	196	47	541	112	907	142	1,150	172	1,393
18	207	48	552	113	915	143	1,158	173	1,401
19	219	49	564	114	923	144	1,166	174	1,409
20	230	50	575	115	932	145	1,175	175	1,418
21	242	51	587	116	940	146	1,183	176	1,426
22	253	52	598	117	948	147	1,191	177	1,434
23	265	53	610	118	956	148	1,199	178	1,442
24	276	54	621	119	964	149	1,207	179	1,450
25	288	55	633	120	972	150	1,215	180	1,458
26	299	56	644	121	980	151	1,223	181	1,466
27	311	57	656	122	988	152	1,231	182	1,474
28	322	58	667	123	996	153	1,239	183	1,482
29	334	59	679	124	1,004	154	1,247	184	1,490
30	345	60	690	125	1,013	155	1,256	185	1,499
31	357	61	702	126	1,021	156	1,264	186	1,507
32	368	62	713	127	1,029	157	1,271	187	1,515
33	380	63	725	128	1,037	158	1,280	188	1,523
34	391	64	736	129	1,045	159	1,288	189	1,531
35	403	65	748	130	1,053	160	1,296	190	1,539
36	414	66	759	131	1,061	161	1,304	191	1,547
37	426	67	771	132	1,069	162	1,312	192	1,555
38	437	68	782	133	1,077	163	1,320	193	1,563
39	449	69	794	134	1,085	164	1,328	194	1,571
40	460	70	805	135	1,094	165	1,337	195	1,580
41	472	71	817	136	1,102	166	1,345	196	1,588
42	483	72	828	137	1,110	167	1,353	197	1,596
43	495	73	840	138	1,118	168	1,361	198	1,604
44	506	74	851	139	1,126	169	1,369	199	1,612

* *Ibid.*

Having obtained these coefficients, it was next possible to compute a formula:

$Bv = 4,530 \times Sa^* - 11.5 \times \text{Age} - 8.1 \times Fi - 600 = \text{fullness index}$, in which Bv = blood volume, Sa = surface area, and Fi = fullness index, and with this we were able to predict with an error of ± 154 c.c., or ± 2.6 per cent, the blood volumes of men with normal builds. The calculations can easily be made with the help of the figures given in Table 12, and the following example will help to make clear how they should be used.

To calculate the probable blood volume of a man, aged twenty-eight, weighing 72 kg. and standing 172 cm. in his stockings, one turns first to the Boothby-Sandiford nomogram (Fig. 4), or to Du Bois' standards and finds that the body surface is 1.85 sq. m. In Table 12 opposite body surface 1.85, there is the figure 7,781 (representing $1.85 \times 4,530 - 600$); and opposite age 28, is the figure 322. To get the fullness index one turns, in a table of cubes, to 172, the height in centimeters, and finds 5,088,448. Dividing 72, the weight in kilograms, by 509, the first three figures of the cubic product, one gets 0.141. Opposite fullness index 141 in the table, one finds the figure 1,142. Adding the two corrections, 322 and 1,142, and subtracting the sum from 7,781, one gets 6,317 which is the predicted blood volume in cubic centimeters.

The close agreement found between calculated and actual values is all the more remarkable in that the error is no larger than that which seems to be inherent to the method, and it would seem now that blood volume in relation to body surface must be one of the most constant features of the human body. This interdependence of blood volume and body surface will be brought out strikingly again in Chapter VI where it will be seen that, although the taking on by the body of a large amount of fat considerably alters the usual relation between blood volume and weight, it does not change very much the relation between blood volume and body surface. In fifteen of the twenty-seven obese persons observed, the long formula predicted the blood volume (from body surface) with an error of from 50 to 700 c.c. or from 0.8 to 13 per cent, and for the group as a whole the error was ± 9.7 per cent.

Doubtless a better formula can be derived when more data are available and partial correlation coefficients have greater significance. There is some evidence also that slightly different formulas will have to be used for men and women and for the obese, but these cannot be calculated with sufficient accuracy. It might also be found better to predict plasma volume and not blood volume, which depends on still another variable, the volume of cells.

* The term "body surface" has been used elsewhere in this monograph instead of "surface area." However, some authors have used surface area, and here, where a symbol and equation are concerned, surface area (Sa) has been retained.

BLOOD VOLUME IN INFANTS AND CHILDREN

Lucas and Dearing, using the dye method, estimated the blood volume and plasma volume in forty-four normal infants aged from two and a half hours to one year. In infants aged fifteen days or less they noted a wide range in the volume of blood according to body weight, 107 to 195 c.c. for each kilogram. The average for this group was 147 c.c. for each kilogram. The plasma volume for each kilogram of weight ranged from 45 to 63 c.c.; so the cell volume must have been abnormally high. Between the ages of fifteen days and one year there was

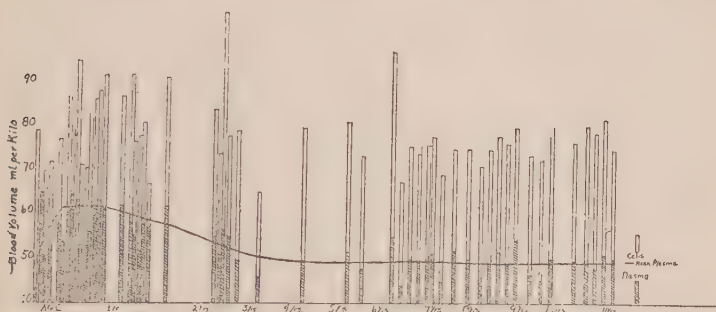


FIG. 5.—The relation of blood volume and plasma volume for each kilogram in normal persons at different ages.—After Darrow, Soule, and Buckman.

a narrower range for the relative volume of blood; the extremes were 90 to 126 c.c., with an average, for this age group, of 109 c.c. for each kilogram. Bakwin and Rivkin, using the dye method, found blood volumes varying from 71 to 148 c.c. for each kilogram, with an average of 101 c.c. The plasma volumes averaged 61 c.c. for each kilogram in infants aged from twelve days to ten months, and varied from 38 to 72 c.c. In nineteen cases the average volume of blood was 1,700 c.c. for each square meter, which is low as compared to values for adults. Marriott and Perkins found blood volumes ranging from 80 to 108 c.c.

for each kilogram in infants under one year of age. In marasmus the values ranged from 48 to 104 c.c.

Darrow, Soule, and Buckman (Figs. 5 and 6) studied blood volume and plasma volume in infants and children up to eleven years. Their observations agree with those of Lucas and Dearing, Bakwin and Rivkin, Marriott, and Perkins. There is a rise in the plasma volume from 50 to 62 c.c. for each kilogram during the first year of life, and a return to 50 c.c. after the

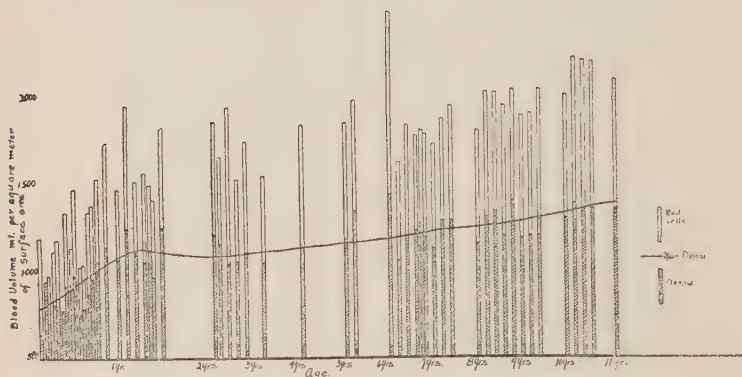


FIG. 6.—The relation of blood volume and plasma volume for each square meter of body surface in normal persons at different ages.—After Darrow, Soule, and Buckman.

fourth year of life. According to body surface, there is a rise from 750 to 1,100 c.c. during the first year and thereafter an increase to 1,375 c.c. at the twelfth year. From these observations, it is apparent that the blood volume according to body weight is relatively much higher in infants than in adults. The plasma volume according to ratios of body weight is moderately higher than those in adults, which indicates a large figure for volume of cells according to body weight. This polycythemia neonatorum was noted by Williamson, Lippman,⁷³ and Hirschfeld, who found high values for hemoglobin

and number of erythrocytes in infants. When compared with body surface, the blood volume of the child is less than that of the adult. The result is that infants seem to have blood volumes too large for their weight, but too small for their body surface. The changes occurring in the blood volume during the second week after birth are of interest, and the reduction in the volume of cells probably indicates a hemolytic crisis, which in turn is probably related to icterus neonatorum.

FLUCTUATIONS OF BLOOD VOLUME AND PLASMA VOLUME IN NORMAL SUBJECTS

The constancy of the blood volume and plasma volume in the same subject was studied in a series of twenty-two normal persons in whom two or more determinations were made after intervals varying from one day to twenty-four months. The studies were made under comparable conditions of rest and room temperature (Table 13). The average individual variation in blood volume for the group was 5.8 per cent. In ten of the twelve of the first group (section A, Table 13, cases with time intervals of two weeks or less) the second determinations were within 5 per cent of the first, which we regard as fairly close and comparable with results obtainable, for example, with a hemoglobinometer. The other ten subjects (section B, Table 13, with time intervals from one month to two years) showed variations of from 1.8 to 29.2 per cent. In one case (Case 16, Table 13) there was an increase of 1,450 c.c. in the blood volume and approximately half of this was represented by plasma. Obviously, with slight changes in the figures for blood volume and plasma volume there were but slight changes in the ratios of these figures to body weight. The average variations in the percentage of cells by the hematocrit and percentage of hemoglobin were 4 per cent each.

The reason for these variations is not clear: some are due

TABLE 13

REPEATED DETERMINATIONS OF BLOOD VOLUME AND PLASMA VOLUME ON
NORMAL SUBJECTS, SHOWING FLUCTUATIONS

Case.	Date.	Age and sex.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Variation, per cent.		Time interval.
					Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Blood volume, c.c. for each kg. of body weight.	Plasma volume, c.c. for each kg. of body weight.	
Section A													
1	12/ 8/24	52, M.	14.5	36	5,920	87	3,200	3,790	56	2,050	+ 6.9	+ 3.5	2 days
	12/10/24		14.6	38	6,310	93	3,410	3,910	58	2,110			
2	11/ 7/24	24, M.	20.7	45	5,540	96	3,570	3,050	53	1,965	- 4.2		2 days
	11/ 9/24		18.2	43	5,340	92	3,450	3,050	53	1,965			
3	11/13/24	29, M.	15.9	40	6,660	98	3,640	4,000	59	2,180	- 3.8	- 8.5	2 days
	11/15/24		15.6	43	6,440	95	3,520	3,670	54	2,000			
4	12/ 4/24	25, M.	15.9	45	7,360	105	4,000	4,050	58	2,200	+ 0.9	+ 1.7	1 day
	12/ 5/24		16.0	43	8,090	115	4,400	4,610	66	2,510			2 days
	12/ 7/24		15.9	44	7,430	106	4,040	4,160	59	2,260			
5	12/ 3/24	22, M.	15.2	41	6,855	100	3,765	4,040	59	2,220	- 1.0		2 days
	12/ 5/24		15.1	40	6,740	99	3,700	4,040	59	2,220			
6	5/26/26	17, M.	16.0	42	5,750	79	3,110	3,330	44	1,800	- 2.5	+ 2.2	3 days
	5/29/26		16.0	40	5,650	77	3,050	3,390	46	1,830			
7	11/30/24	38, M.	15.7	38	5,320	89	3,170	3,300	55	1,960	+ 7.9	+ 3.6	3 days
	12/ 3/24		15.2	41	5,770	96	3,430	3,400	57	2,020			
8	12/13/24	26, M.	16.3	42	5,350	75	3,020	3,100	43	1,750	- 4.0	+ 2.3	4 days
	12/17/24		15.6	39	5,130	72	2,900	3,130	44	1,770			
9	12/ 6/24	24, M.	15.4	44	7,140	89	3,570	4,000	50	2,000	+ 2.0		4 days
	12/10/24		16.5	45	7,270	91	3,640	4,000	50	2,000			
10	11/ 7/24	19, M.	15.7	40	4,940	96	3,200	2,960	58	1,920	+ 2.1	+ 1.7	4 days
	11/11/24		15.5	40	4,980	98	3,240	2,990	59	1,940			
11	4/28/26	27, F.	13.9	36	4,550	85	2,880	2,910	54	1,840	+ 4.7	+ 9.3	1 week
	5/ 6/26		14.2	34	4,700	89	2,980	3,100	59	1,960			
12	4/ 1/26	25, M.	16.4	38	6,000	100	3,430	3,710	62	2,120	+ 1.0	- 3.2	2 weeks
	4/14/26		18.6	40	6,250	101	3,570	3,750	60	2,140			

TABLE 13—*Continued*

REPEATED DETERMINATIONS OF BLOOD VOLUME AND PLASMA VOLUME ON
NORMAL SUBJECTS, SHOWING FLUCTUATIONS

Case.	Date.	Age and sex.	Hemoglobin, gm. in each 100 c.c. of blood.		Cells by hematocrit, per cent.	Blood.			Plasma.			Variation, per cent.		Time interval.
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Blood volume, c.c. for each kg. of body weight.	Plasma volume, c.c. for each kg. of body weight.	
Section B														
13	2/21/24	24, M.	15.7	38	6,020	97	3,460	3,740	60	2,150	— 2.1	— 5.0	1 month	
	3/24/24		15.3	40	6,000	95	3,450	3,600	57	2,070				
14	12/10/24	24, M.	16.5	45	7,270	91	3,640	4,000	50	2,000	— 10.9		2 months	
	2/ 8/25		15.6	38	6,450	81	3,220	4,000	50	2,000				
15	8/20/24	33, M.	18.5	41	5,810	84	3,180	3,430	50	1,880	+ 2.4		3 months	
	11/16/24			42	5,850	86	3,210	3,390	50	1,860				
16	9/ 9/25	25, M.	17.3	43	5,030	72	2,810	2,880	41	1,600	+29.2	+21.7	7 months	
	4/14/26		18.2	45	6,480	93	3,600	3,560	50	1,975				
17	4/14/24	40, M.	16.5	42	4,770	70	2,730	2,770	40	1,580	— 7.1	— 5.0	7 months	
	11/10/24		16.9	42	4,540	65	2,560	2,630	38	1,480				
18	12/17/24	26, M.	15.6	42	5,130	72	2,900	3,130	44	1,770	+11.1	+ 4.5	9 months	
	9/11/25		15.6	42	5,690	80	3,210	3,300	46	1,860				
19	11/12/24	44, M.	18.6	40	5,770	77	3,120	3,460	46	1,820	— 9.1	— 10.8	10 months	
	9/ 3/25		16.1	42	5,440	70	2,880	3,160	41	1,670				
20	11/10/24	40, M.	16.9	42	4,540	65	2,560	2,630	38	1,480	+ 9.2	+13.1	10 months	
	9/ 2/25		15.6	40	5,000	71	2,810	3,000	43	1,690				
21	9/14/24	27, M.	17.3	41	6,100	101	3,500	3,600	60	2,070	— 3.9	— 5.0	1 year	
	9/12/25		18.6	41	5,500	97	3,240	3,240	57	1,900				
22	9/20/23	21, F.	14.2	36	3,760	59	2,290	2,410	38	1,470	+ 1.8	+ 7.9	2 years	
	9/ 6/25		14.2	32	3,730	60	2,320	2,540	41	1,580				

to the inherent error of the method,* but others are probably physiologic, perhaps seasonal; but it is apparent that in the

* After careful consideration of all our data we are inclined to believe that the error of the method is within \pm 5 per cent, and that changes of greater magnitude have true significance.

majority of the cases studied, blood volume and plasma volume were fairly stable and constant.

FLUCTUATIONS OF BLOOD VOLUME AND PLASMA VOLUME IN ANIMALS

It was shown in our laboratories by Dr. John White that there was considerable variation in the blood volume of the dog over moderate intervals of time. The studies were made on healthy animals at intervals of from one to twenty days (Table 14). It is obvious that the blood volume and plasma volume in dogs are subject to greater variation than those obtained in man. The fluctuations seem to be actual, as all factors participate. The hemoglobin varies in about the same degree as the blood volume and the plasma volume.

EFFECTS OF ENVIRONMENTAL TEMPERATURE

In order to obtain more accurate information on the effects of environmental temperature on the blood volume and plasma volume, determinations of the blood volume were made on six normal subjects during periods of excessively cold and excessively hot weather respectively (Table 15). The room temperature was allowed to assume that of the out-of-doors. The first determination was made during the cold period. The room temperature was reduced in one instance to as low as 8.3° C. The subjects were lightly clad and the volume determinations were made after shivering had been induced for thirty minutes. The experiments to determine the effects of environmental heat were carried out in hot weather or, in one instance, with the subject placed in a sweating chamber with temperature up to 44° C. for a period of thirty minutes or more. The volume determinations were made during the period of sweating and when the skin was definitely red. In more than half of the subjects there was a decrease in the blood volume as the result of heat.

TABLE 14
 REPEATED DETERMINATIONS OF BLOOD VOLUME AND PLASMA VOLUME
 SHOWING FLUCTUATIONS AT LONG INTERVALS IN NORMAL DOGS

Dog.	Date.	Body weight, kg.	Cells by hematocrit, per cent.	Total blood volume, c.c.	Blood volume for each kg. of body weight.	Total plasma volume, c.c.	Plasma volume for each kg. of body weight.	Hemoglobin, gm. per cent.
2	1/26/28	5.87	48	669	113.9	348	59.3	16.9
	1/27/28	7.00	55	1,048	149.7	472	67.5	17.4
	1/30/28	6.60	45	821	124.3	452	68.5	13.4
	2/ 4/28	6.37	43	780	122.3	445	70.0	14.5
	2/ 9/28	6.35	37	718	112.8	451	71.0	12.2
	2/13/28	6.25	37	658	104.9	415	66.4	11.9
3	1/31/28	10.40	47	969	93.1	514	49.4	17.2
	2/ 2/28	10.30	44	1,107	107.2	620	60.0	14.9
	2/ 6/28	9.90	47	992	100.2	526	53.1	16.1
	2/10/28	10.60	41	1,108	95.0	654	61.6	15.0
	2/14/28	10.60	40	1,023	96.2	614	57.7	13.8
4	1/25/28	18.75	44	1,977	105.4	1,105	59.2	13.85
	1/31/28	18.38	47	1,684	91.5	893	48.9	15.8
	2/ 2/28	17.95	45	1,472	82.0	810	45.1	14.3
	2/ 6/28	18.05	45	1,683	91.5	926	51.7	15.1
	2/10/28	18.35	41	1,539	82.6	907	49.3	15.7
	2/14/28	18.09	42	1,670	92.5	969	53.5	14.6

In only one subject (Case 3, Table 15) was this marked, a loss of 1,450 c.c. of which 680 c.c. was plasma. In one subject (Case 5) there was a decrease of 750 c.c. of blood in an interval of seventeen months. This was accounted for largely by a loss

TABLE 15.—COMPARATIVE DETERMINATIONS ON NORMAL SUBJECTS DURING PERIODS OF HOT AND COLD WEATHER AND IN HEATING CHAMBER

Case.	Weight, kg.	Age and sex.	Date.	Room temperature, °C.	Barometer reading.	Hemoglobin in each 100 c.c. of blood, gm.	Cells by hematocrit, per cent.	Blood.				Plasma.				Comment.
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.			
1	75	44	11/10/23	18.0		16.0	42	5,740	77	3,100	3,270	43	1,770			
	75	M.	11/12/24	44.0	742	15.8	40	5,770	77	3,120	3,460	46	1,820		Time in chamber, thirty-five minutes; skin just moist.	
	78		9/9/25	24.0	733	16.1	42	5,440	70	2,880	3,160	40	1,670			
2	71	26	12/13/24	8.3	730	16.3	42	5,350	75	3,020	3,100	44	1,750			
	71	M.	9/11/25	16.0	734	15.6	42	5,690	80	3,210	3,300	46	1,860			
	70	25	4/14/24	8.5	733	18.2	45	6,480	93	3,720	3,560	51	1,930			
3	71	M.	9/9/25	22.5	725	17.3	43	5,030	72	2,810	2,880	41	1,600			
	68	40	4/14/24	18.5	733	16.5	42	4,770	70	2,730	2,770	40	1,580			
	69	M.	11/10/24	43.0		16.9	42	4,540	66	2,560	2,630	38	1,480		Time in chamber, thirty minutes; skin just moist.	
4	71		9/9/25	25.0	732	15.6	40	5,000	72	2,810	3,000	43	1,690			
	62	25	4/14/24	19.0	742	18.6	40	6,250	101	3,570	3,750	60	2,140			
	60	M.	11/14/24	45.0		17.3	41	6,100	101	3,500	3,600	60	2,070		Time in chamber, thirty minutes; skin just moist.	
5	57		9/12/25	24.0	738	18.6	41	5,500	96	3,230	3,240	57	1,850			
	68	33	11/16/23	10.0	738	18.6	42	5,850	86	3,210	3,390	50	1,860			
	69	M.	8/20/23	23.0	739	18.5	41	5,810	84	3,180	3,430	50	1,880			

of plasma. In two subjects there were slight increases in the volume of blood at the higher temperatures, but not in a sufficient degree to be significant. The time intervals between the volume studies in this group varied from seven to twenty-two months. Obviously, acclimatization factors are not included in the experiments in which the patients were placed in the heating chamber, because the time interval was of such short duration.

RELATION OF WEIGHT OF BLOOD TO WEIGHT OF BODY

We have in this work followed the usual practice of expressing blood volume as so many cubic centimeters for each kilogram of body weight. This, we believe, is justifiable, provided the true significance of the figures is appreciated. When one wishes to compare the mass of the blood with that of the body, and according to Erlanger this is highly desirable, one multiplies the actual volume in cubic centimeters by 1,056 and obtains the weight of the blood in grams. We question, however, the wisdom of making this calculation in the presence of certain diseases such as anemia and polycythemia vera in which the specific gravity of the blood varies greatly. Unless accurate measurements of that factor are made one is only multiplying a figure about which one is fairly certain by another about which one knows little. For certain purposes, however, the actual volume is preferable because the volume of blood and plasma as distributed in the capillary vessels is significant from the standpoint of metabolic change.

In the original report of Keith, Rowntree, and Geraghty the plasma volumes in eighteen normal subjects varied from 43 to 54 c.c. for each kilogram, with an average of 50 c.c. They found that the total blood volume for fourteen subjects ranged from 78.5 to 99 c.c. for each kilogram with an average of 85 c.c. Herzfeld, with the dye method, found the blood mass to vary from 6.6 to 8.3 per cent of the body weight. Brown and

Rowntree in a study on ten normal subjects found from 72 to 100 c.c. of blood and from 43 to 59 c.c. of plasma for each kilogram of body weight with average values of 88 and 53, respectively. There were from 2,550 to 4,010 c.c. of blood and from 1,425 to 2,250 c.c. of plasma for each square meter, with average values of 3,360 to 2,050 c.c. respectively. Seyderhelm and Lampe, using the dye method, noted an average blood volume of from 82 to 85 c.c. for each kilogram, and plasma volumes of from 44 to 51 c.c. in healthy men. Rusznák, employing the dye method, found an average value of 82.6 c.c. of blood and 44.5 c.c. of plasma for each kilogram of body weight in eleven normal subjects.

From the foregoing statements, it is obvious that many factors enter into the interpretation of blood volume estimations. We believe that in the future blood volume will probably be expressed in terms of body surface. In all probability the normal will be expressed as zero and variation from this as per cent plus or minus, similar to the method employed to express basal metabolism. It is also probable that the normal will differ somewhat for men and women. Such determination has not been attempted at the present time because our observations relate only to one method of determining blood volume and because we have not a sufficient number of determinations to justify an attempt at establishing the normal for women or for the different decades. More work needs to be done also on blood plasma as well as blood volume and also on the ratio of cell volume to plasma volume.

It is also clear that the blood volume in man is larger than heretofore it was believed to be. Welcker's^{109, 110} traditional one-thirteenth of the body weight must be discarded. The blood represents more nearly one-eleventh than one-thirteenth of the body weight while the plasma represents approximately one-twentieth of the body weight.

Chapter VI

VARIOUS DISEASES

Studies are reported concerning more than 250 cases of various diseases, in many of which blood volume determinations were made more than once. Data of other observers on blood volume are also presented, discussed, and compared with our

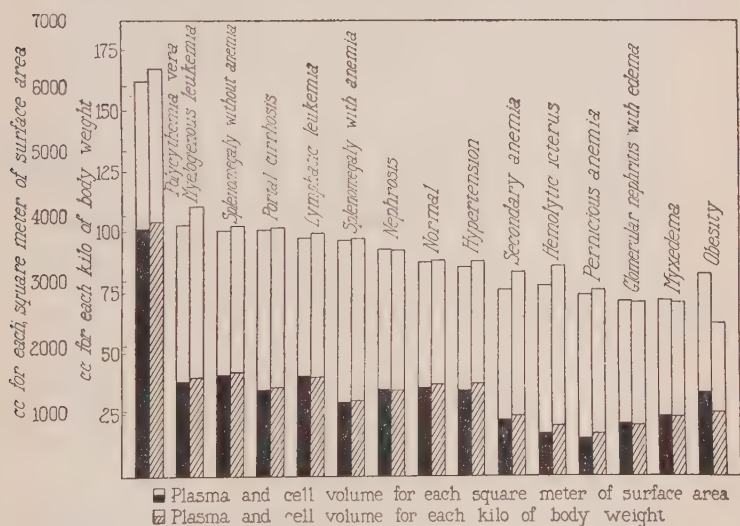


FIG. 7.—Plasma volume and cell volume, each shown in proportion to each square meter of body surface and in proportion to each kilogram of body weight.

own. Some of the results are represented graphically in Figure 7. The subjects in our studies have been grouped according to diseases.

Obesity: Twenty-seven cases representing marked examples of the condition. In eleven of these cases repeated determinations were made during a period of active weight reduction.

Diseases of the blood: (1) Chronic secondary anemia, sixteen cases; (2) pernicious anemia, nine cases; (3) polycythemia vera, fifty cases; (4) atypical or relative polycythemia, three cases; (5) myelogenous leukemia, ten cases, and (6) lymphatic leukemia, four cases.

Diseases of the spleen and liver: (1) Primary splenomegaly without anemia, six cases; (2) cirrhosis of the liver with splenomegaly, nine cases; (3) hemolytic jaundice, eleven cases; (4) primary splenomegaly with anemia, eighteen cases, and (5) chronic infectious splenomegaly and miscellaneous types of splenomegaly, five cases.

Various types of edema (two or more determinations were made before and during the period of diuresis): (1) Acute and subacute glomerulonephritis, twelve cases; (2) nephrosis, nine cases; (3) cardiac edema, eleven cases, and (4) edema of diabetes, three cases.

Diseases of the vascular system: (1) Essential hypertension, ten cases; (2) Raynaud's disease, five cases; (3) thromboangiitis obliterans, six cases; (4) arteriosclerotic disease of the vessels of the leg, with occlusion, three cases, and (5) arteriovenous aneurysm or fistula, seven cases.

Diseases of the endocrine glands: (1) Myxedema, ten cases; (2) hyperthyroidism, four cases; (3) Addison's disease, twelve cases; (4) diabetes insipidus, four cases, and (5) diabetes mellitus, seven cases.

Miscellaneous diseases: (1) Emphysema and chronic bronchitis, twelve cases; (2) pregnancy, thirteen cases, and (3) hemorrhage and shock, twenty-nine cases.⁶¹

NOMENCLATURE AND CLASSIFICATION OF VOLUME STATES

In a former publication,²⁶ we attempted to clarify the nomenclature relating to various blood volume states. Anyone who reads the literature of this subject is confronted with a terminology which defies comprehension. The terms "hydremia," "hydremic plethora," and "plasma plethora" are used to indicate watery dilution or diminished specific gravity of

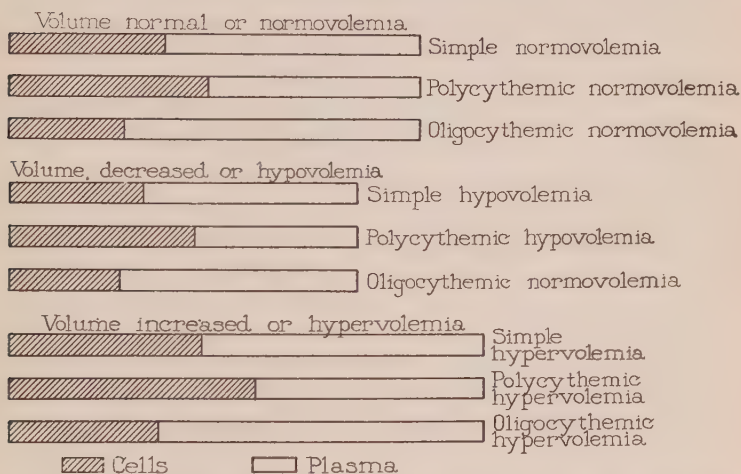


FIG. 8.—The nine possible combinations of the constituents of blood expressed by the new nomenclature.

both the blood and plasma. At times, volume changes are implicated; more frequently, they are not. This confusing situation has arisen from the fact that variation in the volume has been assumed on the basis of variations of single factors or constituents such as the serum proteins, hemoglobin, and specific gravity. Recent work by Linder, Lundsgaard, Van Slyke and Stillman has shown that variations in serum protein may be due to absolute and not to relative changes. The fluctuations may be entirely independent of variation in the blood volume.

The terms "plethora," "polyemia," and "polycythemia" have been used interchangeably to indicate both relative and absolute increase in the cells.

With the advent of a clinical method for determining the volume of blood and plasma, new terms are necessary in order that relative and absolute volume states may be described. On this basis, we presented a simple classification on the nine possible combinations of blood volume, plasma volume, and cell volume. The nomenclature is self-explanatory (Fig. 8).

"Normovolemia"* is used to indicate volume of blood which corresponds to the mean for normal persons of our series: "hypervolemia" to indicate an increase of blood volume above the mean for normal persons, and "hypovolemia" to indicate a decrease of blood volume below the mean for normal persons.

* Objections have been raised against the introduction of additional terms into an already overburdened medical vocabulary. Such objection would be valid if words were available to express these volume relationships. At present there is no suitable term for a small volume of blood. Anhydremia, according to Gould, is a deficiency in the fluid portion of the blood; the volume may be unchanged by an increase in the volume of cells if, at the same time, the fluid portion of the blood is reduced proportionally. To indicate a large volume of blood, many terms have been employed: plethora, hydremic plethora, hydremia, polyemia. The interpretation of these words varies according to the worker. To some, hydremia indicates a percentage increase in the fluid content of the blood, a condition fulfilled by anemia. To others the percentage of fluid in the plasma is increased. Since three factors are involved in the volume status, the cell volume, plasma volume, and the total blood volume, nomenclature indicating these factors is essential. This is illustrated by attempting to state a blood volume condition in which total volume is increased and in which the cell volume is decreased. This can be expressed in the newer terminology as "oligocythemc hypervolemia." The second objection that these terms are hybrids, having Greek and Latin derivations, can best be answered by pointing out the current adoption of many similarly constructed words, as "hypertension," "volumetric," and so forth. Parkes-Weber (1922) called attention to the confusion of terminology in states of the blood. He lamented the absence of an international medical parliament to settle questions of nomenclature.

These three major states of the total volume of blood are each subject to three variations, depending on the ratio of cell volume to plasma volume. The three subgroups are designated by the qualifying terms: "simple," "polycythemic," and "oligocythemic." Figure 8 shows the nine possible combinations of the constituents of blood in the consideration of blood volume. Clinically and experimentally, to correspond with the nine theoretic possibilities, actual variations in the blood volume, plasma volume, and cell volume have been found with the dye method. It must be remembered that this classification does not include a consideration of the number of erythrocytes in relation to their unit percentage of volume. Seyderhelm and Lampe have discussed the condition in which the volume of the individual cell is decreased and therewith there is an increased number of cells for each cubic millimeter of blood without an increase in the total cell volume or blood volume; this is relative polycythemia. The condition does not relate to the state of the blood volume and is not pertinent to the subject at hand.

The question might well be raised as to whether or not the terms "hypovolemia" and "hypervolemia" should be applied to variations from the mean value for normal persons, for instance 87.7 c.c. for each kilogram of body weight, or to variations outside of the usual range of blood volume for normal persons, approximately 80 to 100 c.c. of blood for each kilogram of body weight. We have arbitrarily chosen the former for our purposes because the profession has established certain precedents relating to other body constants. Thus, definite normals have been set: for body temperature, 98.6° F.; for hydrogen-ion concentration for the plasma, pH 7.36; and for basal metabolic rate, approximately 40 calories each hour for each square meter of body surface, arbitrarily expressed as 0 per cent. Such figures emphasize the importance of the mean

for normal persons and of all departures from it. While in the individual case a variation of plus or minus 10 per cent may not have any significance, yet in disease groups, with a mean value plus or minus 10 per cent, this change may assume considerable significance. Thus, our group of cases of secondary anemia yielded a mean total blood volume of 82.8 c.c. for each kilogram of body weight; and our cases of nephrosis, a value of 95.3 c.c. for each kilogram. This we believe to have some significance from the standpoint of these two types of diseases as groups; yet we attach no real significance to such variations from the mean for normal persons in the individual case.

Similarly, and for the same reasons, we have accepted one definite value for plasma volume, 51.2 c.c. for each kilogram of body weight. Such a point of view permits a more definite classification of cases. It also directs attention to all variations from the normal which, in the early development of the field at least, seems highly desirable.

Chapter VII

OBESITY (Table 16)

In this study, seven men and twenty women, some of whom were included in the report of Brown and Keith, all markedly overweight and some suffering from mild degrees of cardiovascular renal disease, were observed. Patients with palpable edema were not included. Obesity had been diagnosed as the primary or essential abnormality in all the cases.

The following factors were determined: (1) The mean values for the total blood volume and for the plasma volume; (2) the mean values for the blood volume and plasma volume according to body weight and body surface; (3) the changes in the blood volume and plasma volume during rapid weight reduction, and (4) the correlation coefficients between blood volume and plasma volume on the one hand, and between body surface and body weight on the other.

As one would expect, both the total plasma volume and blood volume in the obese person averaged higher than in the normal person (Fig. 9). The mean value for blood volume of the obese person was 6,416 c.c., as compared with 5,710 c.c. for the normal person, while the plasma volume was 3,842 c.c. and 3,350 c.c. for the obese person and normal person respectively. With this increase of 12.4 per cent in the volume of the blood and 14.6 per cent in the volume of the plasma there was an increase in body surface of 20.7 per cent and in body weight of 62.4 per cent.

From these figures and from the curves in Figure 9, b and c, one can see that the increase in plasma volume follows closely

TABLE 16

OBESITY

Cases.	Age and sex.	Weight, kg.	Body surface, sq. m.	Height, cm.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.		
							Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	30, F.	64	1.57	148.5	14.9	38	4,300	67	2,740	2,670	42	1,690
2	52, F.	101	2.00	158.5	14.5	44	7,220	71	3,610	4,040	40	2,020
3	45, F.	74.3	1.76	158.5	13.8	39	5,960	80	3,385	3,640	49	2,070
4	42, F.	108	2.14	166.5	13.8	40	5,930	55	2,800	3,560	33	1,670
5	33, F.	104	2.02	157.5		38	5,050	49	2,500	3,130	30	1,550
6	55, F.	87	1.87	157.5	13.7	43	5,900	68	3,150	3,360	38	1,790
7	40, M.	95	2.08	172.7	15.6	41	7,260	76	3,490	4,290	45	2,060
8	41, F.	94	2.06	172.7	15.3	40	6,450	69	3,130	3,870	41	1,880
9	55, F.	120	2.22	165.0	13.8	47	6,530	54	2,940	3,460	29	1,560
10	39, F.	112	2.10	157.5	12.3	47	6,290	56	2,990	3,330	30	1,580
11	60, F.	84	1.84	154.75	12.3	41	5,650	67	3,070	3,330	40	1,810
12	54, F.	92	1.91	157.5	13.0	42	6,040	66	3,150	3,500	38	1,830
13	47, F.	112	2.11	160.0	12.7	39	7,890	70	3,720	4,810	43	2,280
14	46, M.	93	2.12	180.0	16.2	35	5,250	56	2,480	3,410	36	1,610
15	53, F.	140	2.30	158.5	15.3	41	6,500	46	2,820	3,850	28	1,670
16	17, M.	139	2.52	180.0	18.6	40	6,670	48	2,650	4,000	29	1,590
17	19, M.	132.7	2.40	172.7	16.6	40	7,140	54	2,975	4,290	32	1,790
18	37, F.	116.5	2.16	162.5	17.9	43	6,490	56	3,000	3,640	31	1,690
19	45, F.	120	2.24	167.5	12.8	35	7,100	59	3,170	4,610	38	2,060
20	40, M.	105	2.16	172.7	16.2	38	6,600	62	3,050	4,090	39	1,890
21	56, F.	136	2.24	156.2	15.0	39	7,470	55	3,290	4,560	33	2,030
22	56, F.	113	2.14	162.5	13.1	34	6,900	61	3,230	4,560	40	2,130
23	19, F.	113	2.10	157.5	15.5	39	7,870	70	3,750	4,800	42	2,290
24	17, F.	120	2.24	167.5	16.3	39	6,080	51	2,710	3,710	31	1,660
25	28, M.	117	2.26	172.0	18.8	42	7,130	61	3,160	4,140	35	1,830
26	66, M.	100	2.05	170.0	17.1	50	7,910	79	3,860	3,960	40	1,930
27	17, F.	64	1.64	157.0	14.2	36	3,762	58	2,290	2,410	38	1,480
Mean values		107	2.10	164.0	15.0	40.8	6,416	62.3	3,081	3,842	37.3	1,821
Probable error.....		2.6	0.03	1.0	0.2	0.5	129	1.2	51	83	0.74	29

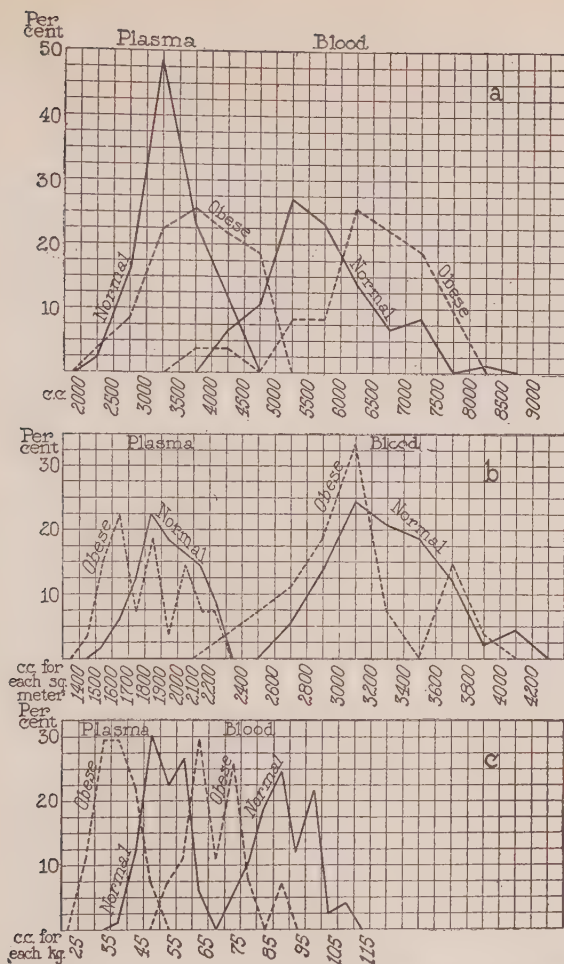


FIG. 9.—a, Curves showing percentage distribution of total plasma volume and blood volume in normal and obese persons. Curves for plasma values are at the left; those for blood values at the right. b, Curves showing percentage distribution of obese and normal persons according to their blood volume and plasma volume for each square meter of body surface. Curves for plasma values are at the left; those for blood values, at the right. c, Curves showing percentage distribution of obese and normal persons according to their blood volume and plasma volume for each kilogram of body weight. Curves for plasma values are at the left; those for blood values, at the right.

the increase in body surface, but lags far behind the increase in body weight. As was pointed out in Chapter V, this failure of

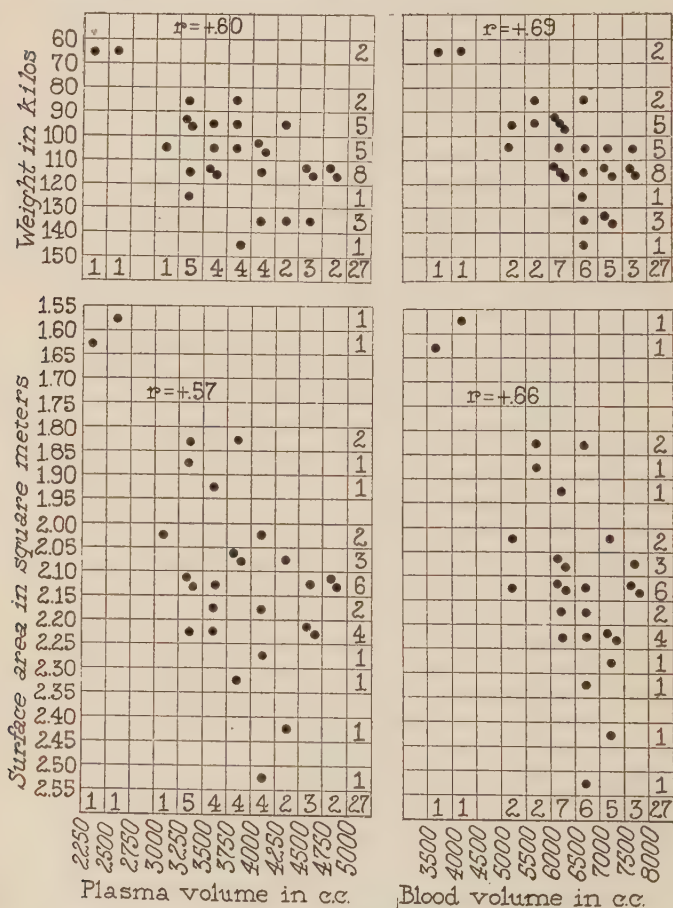


FIG. 10.—The correlation of blood volume and plasma volume with weight and body surface in obese persons.

blood plasma to increase parallel with body weight is probably because fat has a relatively poor blood supply. The fact that

blood volume lags behind plasma volume as compared with the increases in body weight and body surface suggests that the cell volume, by the hematocrit, is a little smaller in the obese than in the normal subject. Actually, the mean value was 40.8 ± 0.5 as compared with 41 in the normal subject. The range of other values and the mean values can be read in Table 16.

That obese subjects are relatively poor in blood and plasma was first shown by Haldane and Smith with the carbon monoxide method and later by Keith, Rowntree, and Geraghty with the dye method. Our data lend little support to the assumption, that sometimes has been made, that a large volume of blood is present in the obese subject, and that hypertrophy of the heart, when present, is compensatory for a large increase in the circulating fluid.

A study of the correlations (Fig. 10) brings out the curious fact that although in the obese subject the relation between blood volume and body surface remains practically the same as that in normal subjects the relation between blood volume and weight is much different.

The variations in the blood volume and plasma volume following rapid reduction of weight have been especially studied by Brown and Keith. Determinations were made on fourteen obese subjects in whom the weight was reduced by from 5 to 15 kg. In five there was an increase in the total plasma volume and in three, a decrease. There was a decrease in the total blood volume in seven. In one there was a decrease in the plasma volume proportional to the decrease in the body weight.

SUMMARY

The mean values for total blood volume and plasma volume are higher (12.4 and 14.6 per cent respectively) in obese than in normal subjects. This increase is not proportional to the

increase in the body weight (which is 62.4 per cent), but is approximately one-fifth for the blood and one-fourth for the plasma. The result is that in comparison with normal subjects, obese subjects have less blood for each kilogram of body weight.

The increase in body surface was 20.5 per cent in cases of obesity as compared to the mean value for normal subjects. Therefore, the increase in blood volume and plasma volume in obesity corresponds more closely to that of body surface than to that of body weight.

In the obese subjects it is much easier to predict blood volume and plasma volume on the basis of body surface than on that of body weight.

With rapid reduction in weight as shown by Brown and Keith, there is no constant variation in amount or direction in the blood volume and plasma volume. Three of eight of the subjects studied showed some decrease in blood volume.

Chapter VIII

DISEASES OF THE BLOOD

CHRONIC SECONDARY ANEMIA (TABLE 17)

Sixteen cases were included in this group: cases of carcinoma, chronic glomerulonephritis without edema, arthritis, and some of unexplained origin. A total of forty determinations was made.

The blood volume for each kilogram of body weight ranged from 53 to 114 c.c., with a mean value of 82.8 c.c. For each square meter of body surface, the blood volume values ranged from 2,300 to 3,900 c.c. with a mean value of 2,840 c.c. In two cases, there was a blood volume of more than 100 c.c. for each kilogram of body weight, with values of 114 and 103 c.c.; in three cases the corresponding values were at the lower limit of normal or below. Two of these patients (Cases 1 and 13) were moderately overweight. The mean volume of blood for each kilogram of body weight was 4.9 c.c. less than the mean for normal persons.

The mean value for the plasma volume for each kilogram of body weight was 58.7 c.c., a value of 7.5 c.c. greater than the mean value for normal persons. In six cases the plasma volume for each kilogram of body weight was 60 c.c. or more, and in only one case was the value unusually low. The mean value for volume of plasma for each square meter of body surface was 1,990 c.c.

The mean value for the volume of cells or the difference between the total blood volume and total plasma volume was

TABLE 17
CHRONIC SECONDARY ANEMIA

Case.	Body weight, kg.	Hemoglobin, gm. in each 100 c.c. blood.	Cells by hematocrit, per cent.	Blood.			Plasma.		
				Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	75	6.8	22	4,690	62	2,570	3,660	49	2,010
2	48	8.7	20	4,090	85	2,770	3,270	68	2,210
3	32	10.3	20	2,670	83	2,300	2,140	67	1,840
4	43	13.9	33	3,750	87	2,620	2,510	58	1,750
5	65	10.5	32	4,270	66	2,550	2,900	45	1,740
6	50	7.0	21	3,800	76	2,480	3,000	60	1,960
7	54		33	6,170	114	3,900	4,130	76	2,610
8	52	13.2	35	5,350	103	3,500	3,480	67	2,270
9	57	10.6	30	4,310	76	2,660	3,020	53	1,860
10	60	13.3	37	5,550	92	3,230	3,500	58	2,030
11	40	8.7	27	3,850	96	2,940	2,810	70	2,140
12	54	12.4	30	4,230	78		2,960	55	
13	67	9.2	27	5,300	79	2,940	3,870	58	2,150
14	45	12.7	36	4,000	89	2,810	2,560	57	1,800
15	43	13.0	37	3,500	81	2,500	2,210	51	1,570
16	84	7.1	26	4,420	53	2,350	3,270	39	1,740
Mean values . . .	55	9.8	29.6	4,406	82.8	2,840	3,100	58.7	1,990
Probable error	2.1	0.4	1.0	143	2	78	93	1.6	46

1,306 c.c. as compared with the mean value for cell volume in normal persons of 2,360 c.c. According to body weight, subtracting plasma volume for each kilogram from blood volume for each kilogram, there were 24.1 c.c. of cells for each kilogram for the cases of anemia, as compared with the mean value for normal persons of 36.5 c.c.

The mean value for hemoglobin was 9.8 gm. per cent (9.0 gm. of circulating hemoglobin for each kilogram of body weight, and 298 gm. for each square meter of body surface). The mean value for the cells by the hematocrit was 29.6 per cent.

The mean blood volume in these cases of secondary anemia in relation to each kilogram of body weight was within the range of normal but less than the mean value for normal persons. The mean value for plasma volume for each kilogram was moderately increased to about 14 per cent over the mean value for normal persons. The volume status indicates oligocythemic hypovolemia. There were two significant examples (Cases 7 and 8) of oligocythemic hypervolemia, in which the increased volume was due largely to excess of plasma. In the series of secondary anemia as a whole the mean value for cell volume for each kilogram of body weight was decreased to about 33 per cent less than the mean for normal persons, with a mean increase of 15 per cent in the plasma volume for each kilogram of body weight.* This indicates an inadequate replacement with plasma to compensate for the decreased amount of cells.

Keith, Rowntree, and Geraghty found a definite increase in the volume of plasma (60 c.c. or above) in relation to body weight in four of eight cases of secondary anemia. Mendershausen and Herzfeld, using the dye method, found an absolute decrease in the total blood volume and cell volume, with

* The cell volume for each kilogram of body weight or each square meter of body surface is obtained by subtracting the plasma volume from the blood volume.

plasma volume ranging from 43 to 84 c.c. for each kilogram of body weight.

All these studies show that considerable variation exists in the blood volume and the plasma volume in cases of secondary anemia. In all but two cases (Cases 7 and 8, Table 17) the total cell volume and the cell volume relative to body weight were reduced. In Case 7, for each kilogram of body weight, the blood volume was 114 c.c., the plasma volume 76 c.c. and the cell volume 38 c.c. In Case 8 for each kilogram of body weight, there were 103 c.c. of blood, 36 c.c. of cells, and 67 c.c. of plasma. There was moderate reduction below the mean for normal persons in the amount of hemoglobin in each 100 c.c. According to the mean values there was 7.8 gm. of hemoglobin for each kilogram of body weight. These cases (Cases 7 and 8) clinically represented examples of mild chronic secondary anemia, and as compared with normal data the cell volume according to body weight was 50 per cent of that for normal persons. If the volume of hemoglobin is calculated in Case 8 by the formula:

$$\frac{\text{total blood volume} \times \text{per cent grams of hemoglobin}}{\text{body weight}}, \text{ a value of}$$

13.6 gm. of hemoglobin for each kilogram of body weight is obtained which, as compared to the mean value of 13.8 gm., is only slightly decreased.

The replacement factor, which is the ratio of increase of plasma to loss of cells, was determined for the group. The mean cell volume for each kilogram of body weight was 24.1 c.c. This is 12.4 c.c. or approximately 33 per cent less than the mean for normal persons. The mean plasma volume for each kilogram of body weight was 58.7 c.c., an increase of 14 per cent over the mean for normal persons. The ratio of plasma increase to cell decrease as expressed in per cent would be 42, which is higher than in primary anemia. This is designated as the plasma replacement factor.

PERNICIOUS ANEMIA (TABLE 18)

Nine subjects representing typical examples of pernicious anemia were studied. The mean value for hemoglobin was 10.3 gm. in each 100 c.c. (6.8 gm. for each kilogram and 281 gm. for each square meter). The mean value for the cells by the hematocrit was 22.6 per cent. The mean blood volume was 76.4 c.c. for each kilogram of body weight, or 2,772 c.c. for each square meter of body surface. The range was from 65 to 89 c.c. of blood for each kilogram and from 2,470 to 2,990 c.c. for each square meter. The mean value for plasma volume was 58.8 c.c. for each kilogram or 2,195 c.c. for each square meter. The range was from 49 to 69 c.c. for each kilogram of body weight and from 1,900 to 2,660 c.c. for each square meter of body surface.

TABLE 18
PERNICIOUS ANEMIA

Case.	Age and sex.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes, in each cu. mm., millions.	Cells by hematocrit, per cent.	Blood.			Plasma.			Cells.
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	62, M.	60	9.7	2.49	25	4,740	80	2,850	3,550	60	2,140	1,190
2	54, M.	56	11.3		29	4,970	89	2,990	3,530	63	2,120	1,440
3	53, M.	65	9.8	2.23	20	5,060	78	2,870	4,050	62	2,300	1,010
4	62, M.	67	6.9	1.35	11	5,180	77	2,990	4,610	69	2,660	570
5	57, M.	61	13.8	3.66	31	5,020	82	2,930	3,460	57	2,020	1,560
6	44, M.	77	8.4	2.27	20	5,420	70	2,880	4,340	56	2,310	1,080
7	45, M.	61	12.5	1.90	14	4,500	74	2,470	3,870	63	2,130	630
8	51, M.	74	10.0	1.76	24	4,780	65	2,500	3,640	49	1,900	1,140
9	47, M.	67	10.1	2.26	25	4,530	68	2,530	3,400	51	1,900	1,130
Mean values..		66.4	10.3	2.19	22.6		76.4	2,772		58.8	2,195	
Probable error.....		1.3	0.4	1.6	1.3		1.4	42		1.4	48	

Keith, Rowntree, and Geraghty reported observations on three cases of primary anemia. In one, for each kilogram of body weight, there was a plasma volume of 72 c.c. and a blood volume of 81 c.c.; in the next case the plasma volume was 54 c.c., and blood volume 66 c.c. In the third, a plasma volume of 53 c.c. was found. Denny estimated the blood volume in ten cases of primary anemia by determining the oxygen capacity of the blood before and after transfusion, thus calculating the blood volume. He found values comparable to those obtained by the dye method. In comparison with the mean values for normal persons, the volume of blood was reduced in eight cases, but the plasma volumes were slightly increased, averaging 56 c.c. for each kilogram. Smith,⁹⁹ using the carbon monoxide method, found that the total volume of hemoglobin was reduced in proportion to the severity of the disease, and the plasma volume may be either increased or diminished. Mendershausen, using Congo-red, found the blood volume to be reduced in the active stage of pernicious anemia. During remissions, the volume is normal or subnormal. Mendershausen stated: "If one takes into consideration how much the blood volume depends on the general physical condition, one will find that there can be a decrease also with apparently normal values, namely, when the proportion found between the blood volume and body weight does not correspond to that of a healthy man of the same physical condition." Using the dye method, Herzfeld found the average volume of blood low in primary anemia, 5.5 per cent of the body weight.*

According to our mean values, oligocythemic hypovolemia is the rule in this disease. The individual data in seven of the

* Murphy, Monroe and Fitz, in a recent study (Jour. Am. Med. Assn., 1927, lxxviii, 1211-1214) of patients with pernicious anemia who were treated with liver, found that the plasma volume remained fairly constant whereas the cell volume consistently increased.

nine subjects show that the blood volume according to body weight was within the range for normal persons (70 to 100 c.c.*); two had low blood volume, 65 and 68 c.c., respectively. When these values are compared with those obtained in the cases of chronic secondary anemia, certain differences are noted. The mean hemoglobin in grams per cent is approximately the same for both groups, but the percentage of cells by the hematocrit is lower in the cases of primary anemia, a percentage difference of the mean values of 7.0, indicating a larger saturation value for the hemoglobin in the cases of primary anemia. The plasma volumes are essentially the same in the two types of anemia if the probable error is considered. Therefore, it would be expected that the mean blood volume would be lower in the cases of pernicious anemia, as it is, 76.9 c.c. as compared to 82.8 c.c. for each kilogram of body weight.

Keith⁶¹ and others have shown in the anemia secondary to acute bleeding that following hemorrhage there is an influx of plasma fluid into the blood, thus restoring a part, but rarely the entire volume, of the whole blood. This no doubt is a compensatory process for maintenance of the circulation. It has been demonstrated also, in cases of polycythemia vera under treatment, with a sharp decrease in the volume of cells, that the volume of the plasma increases to some extent. In these cases, the original blood volume is excessively large and it is not necessary that the original blood volume be maintained. Therefore further investigation is required to explain the influx of plasma or tissue fluids in the blood stream. With comparable grades of anemia the markedly high volume of plasma observed in cases of splenic anemia is striking and seems to constitute

* For practical purposes, we kept in mind these figures as the limits of the range for normal persons, because more than 95 per cent of the normal persons came within these limits. In an occasional instance, values were found, among normal persons, which were higher or lower than these values, but they were not considered significant.

an essential distinction between the splenic and nonsplenic types of anemia.

If the replacement factor is calculated in the cases of pernicious anemia the following is found: a mean cell volume of 17.7 c.c. for each kilogram of body weight which, compared with the mean value for normal persons of 36.5 c.c., is a decrease of 51 per cent. The mean plasma volume for each kilogram of body weight of 59.2 c.c. is 8 c.c. higher than the corresponding mean value for normal persons or an increase of about 16 per cent in plasma, giving a replacement factor of 30 per cent, which is low. These data, although only approximate and dealing with a small group of cases, seem to show a more adequate replacement by plasma in cases of secondary anemia as compared with the cases of primary anemia.

POLYCYTHEMIA VERA (TABLE 19)

In the study of blood volume and plasma volume in the diseases of the blood and hematopoietic system, the observations in polycythemia vera have thrown additional light on the nature of the disturbances in this disease. In fifty cases of polycythemia vera one or more determinations were made of the blood volume and plasma volume. In several cases, from four to six determinations were made during the course of treatment with phenylhydrazine (Fig. 11). The diagnosis of polycythemia vera in these cases was based on the increased number of erythrocytes, the abnormally high values for hemoglobin, the viscosity, and the percentage of cells as determined by the hematocrit. The essential observations at general examination included enlargement of the spleen and often enlargement of the liver. The skin and mucous membranes were of the typical brick red or reddish cyanotic appearance. The vessels of the retina and skin were dilated. A case was not in-

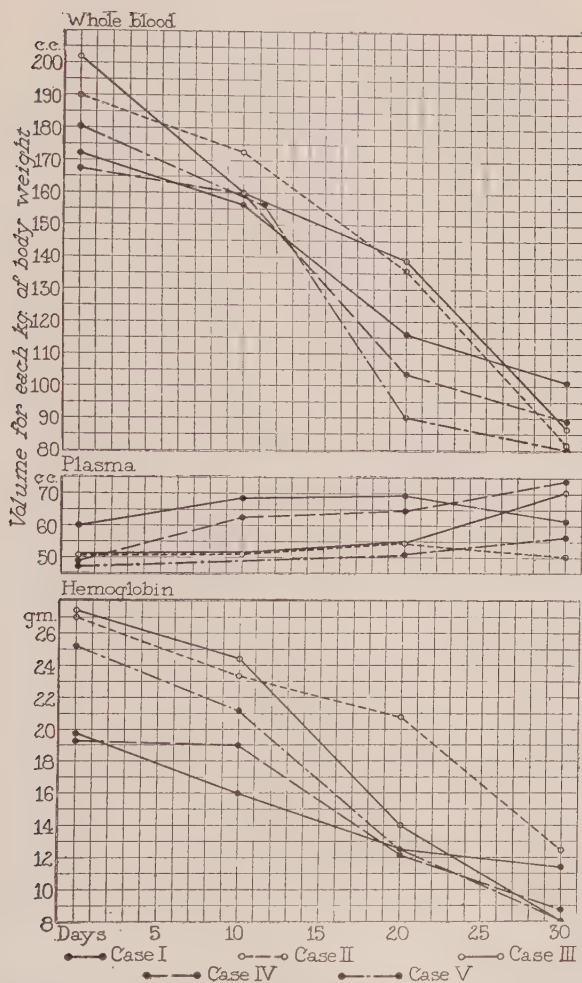


FIG. 11.—Curves showing, in polycythemia vera, effect of rapid destruction of blood on the volume of blood and plasma and on the concentration of the hemoglobin.

TABLE 19
POLYCYTHEMIA VERA

Case.	Age and sex.	Cells by hematocrit, per cent.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes in each cu. mm., millions.	Enlargement of spleen, graded 1 to 4.	Viscosity of blood.	Blood.			Plasma.		
							Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	43, M.	69	27.4	7.84	2	16.0	13,340	202	7,890	4,140	63	2,450
2	68, M.	65	27.5	7.72	2*	14.0	13,710	224	7,740	4,800	78	2,710
3	64, M.	60	21.1	5.76	2 (firm)	18.0	8,560	136	5,200	3,430	55	2,070
4	55, M.	75	26.0	7.00	1	16.0	14,700	180	7,460	3,670	45	1,860
5	62, M.	67	22.5	6.42	1 (hard)	13.2	11,000	184	6,490	3,640	61	2,140
6	42, M.	67	23.5	8.56	1	12.0	11,360	140	5,890	3,750	46	1,940
7	38, F.	63	21.5	7.50	3 (hard)	9.6	10,290	206	6,640	3,810	76	2,460
8	50, M.	65	22.6		1		12,500	179	6,660	4,390	63	2,330
9	51, M.	60	20.0	6.48	2		12,000	190	7,020	4,800	76	2,800
10	56, M.	70	22.9	7.15	1		14,810	210	7,840	4,440	63	2,360
11	63, M.	60	20.4	6.95	2	9.2	10,090	136	5,480	4,140	55	2,250
12	55, F.	69	20.4	9.11	2	9.8	9,220	170	6,230	2,880	53	1,950
13	31, F.	71	23.3	6.89	3 (hard)		7,830	167	5,440	2,975	63	1,560
14	56, M.	72	29.4	8.53	1 (hard)	11.2	12,400	194	7,090	3,460	54	1,980
15	58, M.	47	19.0	5.00	1	10.4	8,500	121	4,540	4,500	65	2,400
16	50, M.	76	25.0	8.39	2	20.6	14,160	205	8,050	3,400	49	1,930
17	43, M.	65	26.4	6.45	1	9.2	9,520	146	5,380	3,330	51	1,880
18	55, M.	56	25.6		3		7,680	174	5,000	3,380	71	2,200
19	52, F.	69	27.1	8.90	2	18.0	10,460	222	6,750	3,240	69	2,090
20	62, F.	48	18.1	6.40	1 (soft)	17.6	8,600	130	5,180	4,470	68	2,690
21	44, M.	62	23.0	7.41	2 (tender)	10.2	9,760	165	5,740	3,710	63	2,180
22	47, M.	65	22.6	8.93	2	11.2	11,300	182	6,730	3,950	64	2,350
23	53, M.	52	24.6	5.82	†	7.8	9,520	161	5,670	4,570	78	2,720
24	61, F.	58	23.7		2		8,170	154	5,340	3,430	65	2,240
25	59, M.	60	24.2	7.50	1 (firm)	9.4	10,840	160	5,830	4,340	64	2,330

* Enlargement of liver, graded 1.

† Right renal tumor.

TABLE 19—Continued

POLYCYTHEMIA VERA

Case.	Age and sex.	Cells by hematocrit, per cent.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes in each cu. mm., millions.	Enlargement of spleen, graded 1 to 4.	Viscosity of blood.	Blood.			Plasma.		
							Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
26	56, M.	70	26.0		1 (firm)		12,245	204	7,285	3,673	61	2,185
27	52, F.	56	22.0	5.99	3	7.5	7,580	152	5,220	3,330	67	2,290
28	62, M.	69		7.34	1 (hard)	10.4	11,260	173	6,470	3,490	54	2,000
29	54, M.	57	20.8	6.24	1	9.0	8,630	144	5,200	3,710	62	2,230
30	56, M.	66	25.5	7.26	1	13.8	13,880	228	7,850	4,720	77	2,660
31	60, M.	58	18.1	7.64	1 (firm)	9.6	10,930	163	6,040	4,590	67	2,540
32	39, M.	66	28.4	7.65	2	14.8	11,450	149	6,060	3,890	51	2,060
33	56, M.	60	20.7	6.34	3		11,250	168	6,360	4,500	67	2,540
34	36, F.	60	15.6	5.76	1	8.8	7,630	153	5,020	3,050	61	2,000
35	25, M.	52	16.1	6.04	1		7,660	128	4,580	3,675	61	2,200
36	63, F.	53	18.7	5.80	1	7.2	7,750	165	5,610	3,640	77	2,635
37	59, M.	61	21.0	6.29	2	8.2	9,060	129	4,810	3,530	50	1,875
38	43, M.	60	25.1	7.09	1	9.8	9,900	177	6,190	3,960	71	2,475
39	62, F.	62	23.2	7.33	3	15.0	9,440	145	5,520	3,490	54	2,040
40	59, M.	65	18.5	5.84	1	10.6	12,400	206	7,200	4,340	72	2,520
41	65, M.	56	20.8	6.04	1	10.4	9,870	132	5,085	4,340	58	2,240
42	67, M.	63	27.8	7.66	2	14.2	9,540	137	5,400	3,525	50	1,990
43	40, M.	44	15.9	4.97	1		9,200	123	4,735	5,150	68	2,650
44	68, F.	51	18.0	5.07	3	6.1	7,200	131	4,800	3,530	64	2,350
45	58, F.	55	14.4	6.24	1	8.4	7,610	127	4,620	3,425	57	2,075
46	48, F.	47	17.1	7.14	3	5.6	8,600	165	5,200	4,560	88	2,760
47	47, M.	60	28.5	5.77	1	10.0	9,480	135	5,100	3,790	53	2,040
48	35, F.	65	20.8	7.24	2		8,350	144		2,925	50	
49	45, F.	57	18.2	6.08	1	8.8	8,360	137	5,320	3,600	59	2,290
50	50, M.	72	29.0	7.10	3	15.0	16,000	246	8,660	4,500	70	2,430
Mean values..		62	22.6	6.89		11.6		167	6,056		63	2,266
Probable error.....		7.02	0.36	1.00		0.38		3.01	100.6		0.89	27.6

cluded if there was clinical evidence of cardiac or pulmonary disease in which a compensatory or secondary type of polycythemia would result. The diagnoses in these cases were made independently by us and by the clinicians in the Section on Clinical Hematology.

The number of erythrocytes ranged from 4,970,000 (Case 43) to 9,110,000 (Case 12) with a mean value of 6,890,000 for each cubic millimeter. The hemoglobin values varied from 14.4 to 29.4 gm. per cent, with a mean value of 22.6 gm. per cent. According to body weight, the blood volume varied from 121 to 246 c.c. for each kilogram, with a mean value of 167 c.c. Relative to body surface the blood volume varied from 4,540 to 8,660 c.c. or a mean of 6,056 c.c. for each square meter. The relative plasma volume varied from 45 to 88 c.c. with a mean of 63 c.c. for each kilogram of body weight; and from 1,560 to 2,800 c.c. with a mean of 2,266 c.c. for each square meter. The mean value for plasma volume in relation to body weight was above the upper limit of normal, 12 c.c. higher than the mean values for normal persons. Excessively large blood volume is due primarily to the increase in the circulating erythrocytes. The hematocrit values are uniformly high; the mean was 62.0 per cent of cells (mean for normal persons, 41 per cent). The lower values for blood volume and plasma volume relative to body weight are observed in cases of polycythemia vera with obesity. This combination, however, has not been common.

Smith and McKisack (1902), using the carbon monoxide method, demonstrated a well marked increase in the blood volume in a boy aged twelve years, with chronic cyanosis and chronic pericarditis. They showed that the blood volume was about twice that for the normal standard. In a case of polycythemia vera studied by Parkes-Weber, the blood volume was ascertained by the carbon monoxide method and was found to

be greatly increased. Similar studies by Acland and Haldane, as quoted by Parkes-Weber, in a case which clinically was polycythemia vera, revealed that the blood volume was two and a half times the normal. Observations of this type have been reported by Boycott and Douglas, who used the carbon monoxide method. Keith, Rowntree, and Geraghty reported observations on two cases of polycythemia. In the first case, there was a high erythrocyte count but the plasma volume and blood volume were only 39 and 73 c.c. for each kilogram of body weight, respectively. These values for blood volume and plasma volume are within the range for normal persons, but are below the mean for normal persons. This case probably was not one of polycythemia vera, but more likely was an example of polycythemic hypovolemia. The high cell count was due to the fact that the proportion of cells to plasma was increased, and the total volume decreased. The second case was probably a true example of mild polycythemia vera. The total blood volume was 113 c.c. for each kilogram of body weight and the plasma volume 60 c.c. for each kilogram. These values are only moderately increased when compared with the mean volume values in the cases of polycythemia vera in this report. Bock, using the dye method, found increased values for volume of blood according to body weight in three cases of polycythemia vera. The relative plasma volume was increased in one case. Brown and Giffin²² reported the blood volume and plasma volume in fourteen cases of polycythemia vera, correlating the disturbances in the vascular system with the large volume of blood. They found that the engorgement of surface capillaries disappeared with decrease of the blood to approximately 110 c.c. for each kilogram. These workers²³ in another study showed that with reduction of the cell volume under treatment with phenylhydrazine, the decrease in the blood volume followed, proportionately, the fall in hemoglobin (Fig. 11), in erythro-

cytes, in the percentage of cells by the hematocrit, and in the viscosity of the whole blood. With reduction of the cell volume, there was slight to moderate increase in the actual and relative plasma volume.

The differentiation of the cases of polycythemia vera from the cases of relative polycythemia is possible by volume determinations. In the latter group, the total blood volume and plasma volume are decreased or normal, but the number of erythrocytes and the percentage of cells, as determined by the hematocrit, may be high. In polycythemia vera, the cell volume and blood volume, both total and relative to body weight and body surface, are markedly increased, and the volume status is designated as polycythemic hypervolemia. In relative polycythemia, the volume status is usually that of polycythemic normovolemia.

The recognition of the large increase in the circulating volume of cells is necessary to make clear the signs and symptoms characteristic of this disease. The distention of the venous portion of the vascular system, and the enlarged spleen and liver, give clinical evidence of the increased circulating mass of blood. The surface vessels are engorged on the venous side of the capillary loops and occasionally this extends over to the arterial segment. The retinal veins are engorged. The experimental work of Krumbhaar and Chanutin on induced plethora showed the tendency of the plasma volume to remain constant and the adaptability of the vascular system to large increases in the blood volume. In polycythemia vera, the viscosity of the blood is high, and the flow of blood, as visualized through the skin capillaries, is slow. Slight changes in environmental temperature produce stasis and cyanosis of the capillary blood. The symptoms of intolerance to heat (vertigo, headache, cerebral irritability, and intravascular thrombosis) may be explained on the basis of the intravascular engorgement. Harrop and

Heath compared these symptoms with those observed in conditions accompanied by anoxemia.

Hartwich and May, using the dye, trypan red, determined the blood volume in four cases in which there was a high percentage of hemoglobin and a high erythrocyte count. In three, the characteristic high values for the volume of blood were found: 142, 180, and 191 c.c. for each kilogram of body weight. The plasma values were low in two cases and increased in one case. The values obtained in the remaining case were inexplicable and according to our experience are unique. They found with an erythrocyte count of 10,400,000 for each cubic millimeter and 92 per cent of cells by the hematocrit (a value suggesting incomplete centrifugalization) 44 c.c. of blood and 3.5 c.c. of plasma for each kilogram of body weight. Following treatment by roentgen ray, there were 9,000,000 erythrocytes for each cubic millimeter, 82 per cent of cells by the hematocrit, and 47 c.c. of blood, and 8.6 c.c. of plasma for each kilogram of body weight. These data suggest errors in technic or in calculation. In our experience the highest value for the percentage of cells by the hematocrit in the living subject has been 76.

All available data concerning the volume of blood in cases of polycythemia vera show a large absolute increase in the number of cells. The cases reported by Boycott and Douglas, and Haldane, using the carbon monoxide method, indicate an increase in the absolute hemoglobin values from two to three times that for the probable normal standard. These studies on polycythemia vera revive the old conception of plethora (hypervolemia), thought erroneous since the experimental work of Wörm-Mueller and Cohnheim. Their experiments indicated that persistent increases in the blood volume could not be produced in the experimental animal. When blood, to the amount of approximately 80 to 100 per cent of the estimated blood volume, was injected into the animal, half of the fluid left the

circulation within half an hour. The cells remained, leaving transitory polycythemia which disappeared within two days. As Parkes-Weber has stated, the condition obtaining in the experimental animal does not correspond with that found in cases of polycythemia vera in the human subject. In the latter, the balance between blood formation and blood destruction is disturbed. There is, in effect, a continued transfusion of blood cells into the organism over long periods. A compensatory mechanism for increased blood destruction, if called into action, is inadequate.

SECONDARY FORMS OF POLYCYTHEMIA

Polycythemia occurring at high altitudes.—Harrop, in his excellent recent review, has suggested classifying cases of polycythemia in two groups: cases due to lowered oxygen tension in the circulating blood or tissues, and cases due to some other frequently unknown cause not directly the result of a low oxygen tension in the blood or tissues. The most striking example of the first group is the polycythemia observed at lowered pressures of oxygen and reduced barometric pressures. The response of the blood in man at high altitudes has been studied by a number of observers, the first of whom was Viault who, in 1899, made observations at an elevation of 4,392 meters. The erythrocyte count in his subject varied from 7,500,000 to 8,000,000 cells. Bert had shown previously, in 1882, that the blood of the Peruvian llama had a very high oxygen capacity. Lippmann⁷⁴ recently reported a 20 per cent increase in the erythrocytes and hemoglobin in natives of Davos at a rather low altitude, 1,560 meters, together with an increase in the total blood volume. Still more recent studies by Dallwig, Kolls, and Loevenhart, and Campbell, on animals kept at normal barometric pressures, but at low oxygen pressures, emphasize the relationship between the degree of anoxemia

and the subsequent polycythemia which develops. As Harrop has noted, it is important to emphasize the many marked individual variations that are found. The response of man to low oxygen tension in the gas cabinets and to rebreathing of gas mixtures containing low percentages of oxygen has been carefully studied and there is complete agreement as to the appreciable increase in the hemoglobin and in the concentration of erythrocytes. This has been studied by Gregg, Lutz, and Schneider, and by Schneider. Harrop has called attention to the fact that there are apparently two stages in the production of erythrocytosis resulting from exposure to high altitudes. The first stage is that which appears rapidly, is not attended by evidence of formation of new blood, and is probably due to expression of erythrocytes from the spleen. The second stage is that which appears only after a longer sojourn at a high altitude and is evidenced by the presence of newly formed erythrocytes in the circulating blood, as shown by many observers. Barcroft⁷ has shown that the maximal number of reticulocytes appears after a residence of about one week at a high altitude.

The question as to whether the increase in the erythrocytes and hemoglobin is relative and is brought about by the abstraction of plasma, or apparent by redistribution of inactive cells, or absolute by the addition of more cells to the circulation has not been definitely proved. Work has been carried out, particularly in the Pike's Peak expedition in 1911, which showed that the percentage of hemoglobin and blood corpuscles, the total oxygen capacity, or the total amount of hemoglobin, increased with lower oxygen pressures at higher elevations. In this expedition, blood volume determinations, as carried out by the carbon monoxide method, showed some increase.

Smith, Belt, Arnold, and Carrier concerned themselves particularly with the changes in the volume of plasma and erythrocytes caused by periods of short residence at high altitudes.

They determined the plasma volume by the dye method, using brilliant vital red, and the volume of erythrocytes and the total hemoglobin of the body by the carbon monoxide method. They also determined the blood volume indirectly, as in the original dye method, by calculation from the hematocrit values. They found an average increase in the erythrocytes for each cubic millimeter of blood of 12 per cent within three weeks of the beginning of residence at an elevation of 11,000 feet, and an average rise in hemoglobin of 14 per cent. By the carbon monoxide method, the total cell volume increased on an average of 19 per cent. There were not any significant variations in the absolute plasma volume as the result of lower pressures of oxygen. The percentage of cells by the hematocrit increased less than the number of erythrocytes and the percentage of hemoglobin, indicating that the cells had become smaller but that the saturation with hemoglobin had not changed. They concluded that the increase in number of cells and in the percentage of hemoglobin is absolute, due to the production of more cells.

From these studies it is apparent that altitude causes increase in the number of cells for each cubic millimeter and in the actual cell volume and blood volume although there are marked variations in the individual responses. The increases in these values with short periods of residence are not marked and do not give evidence of polycythemia of a degree to be confused with the high volumes of blood observed in polycythemia vera. In the studies of Smith, Belt, Arnold, and Carrier, the total blood volume, as determined by the dye method, did not change in two subjects, decreased in two and there was no change in one subject. The blood response as shown in the average values for the five subjects is one of polycythemic normovolemia.

Harrop and Heath, in a recent study of pulmonary gas diffusion in polycythemia vera, presented some evidence that functional obstruction in the lungs to gaseous permeability

occurs in this disease, and that there is consequent lowered oxygen tension in the arterial blood. They advanced the theory that the lowered oxygen tension in the bone marrow acts as a stimulus for the production of erythrocytes. The studies of Lemon on the blood changes in cases of chronic pulmonary diseases and lowered oxygen tension of the arterial blood, did not show increases in the total blood volume and the total cell volume. This is evidence of the inability of chronic anoxemia to produce absolute forms of polycythemia. Further data bearing on this point were, the normal values for oxygen tension which were found in two cases of uncomplicated polycythemia vera. This is discussed more fully in Chapter XIII.

Polycythemia due to pulmonary or cardiac abnormalities.—Polycythemia as determined by the concentration of erythrocytes and hemoglobin has been found in many cases in which there are disturbances of the pulmonary oxygen exchange or by obstructive lesions of the air passages. The polycythemia of congenital heart disease and pulmonary stenosis also has been noted. Fromherz has shown that enlargement of the liver and spleen can occur in this condition. Counts as high as 13,900,000 have been described. Information regarding the status of the blood volume and plasma volume in these forms of secondary polycythemia is not available. The work of Lemon (Chapter XIII) in cases of pulmonary emphysema and bronchitis with cyanosis has shown only occasionally moderate increases in the volume of circulating blood found. The number of circulating erythrocytes never was so high as that in polycythemia vera. We have not carried out any studies in cases of congenital heart disease.

There is another type of case in which an increased concentration of erythrocytes in the peripheral blood has been reported. These are the cases of Ayerza's disease, a condition which first was described in 1901 by Professor Ayerza of Buenos

Aires and which was made the basis of a monograph by Arrillaga. In these cases there is clinical evidence of pulmonary emphysema, hypertrophy of the right side of the heart, and cyanosis frequently of such an extreme degree that the term "cardiacos negros" has been applied to the patients who have the disease. The underlying disturbance in Ayerza's disease was thought to be due to syphilis of the pulmonary artery with obstruction of the pulmonary circulation and deficient oxygenation of the pulmonary blood. Sclerosis of the pulmonary artery seems to be the usual pathologic change in these cases. To our knowledge, studies of the blood volume have not been made. The number of erythrocytes in the peripheral blood frequently is high. Counts as high as 10,000,000 or 11,000,000 for each cubic millimeter have been reported. We have noted one case which apparently would fall in the group of Ayerza's disease.

The patient, a woman aged forty-six years, a few days after a short sojourn at Pike's Peak, manifested symptoms of acute cardiac insufficiency, marked dyspnea, and cyanosis. When she was seen at The Mayo Clinic six months later the conditions found were extreme myocardial insufficiency, extreme dyspnea, and cyanosis, to such an extreme degree as to suggest pigmentation. Generalized telangiectasis had developed over the trunk and legs. The percentage of cells by the hematocrit was 48. The blood volume was 114 c.c. for each kilogram of body weight, and the plasma volume was 59 c.c. for each kilogram of body weight. The number of erythrocytes was 4,520,000 for each cubic millimeter and there were 16.9 gm. of hemoglobin for each 100 c.c. of blood. The oxygen content of the arterial blood was 16.8 volumes per cent, or a saturation of 74.8 per cent. The course of this patient was followed after she left the hospital; she died six months later from cardiac failure. Necropsy was not obtained.

The data in this case clinically suggest the condition described by Ayerza, and indicate lower percentage saturation with oxygen of the arterial blood, without increase in the concentration of erythrocytes in the peripheral blood, but with definite increase in the total circulating blood and in the percentage of cells by the hematocrit. It would seem that in an extreme degree of anoxemia such as this patient presented, the volume increase was only moderate and in no way compared to those found in polycythemia vera.

Geisböck's syndrome (polycythemia hypertonica).—Cases have been described by Geisböck characterized by a percentage increase in the erythrocytes, and high values for the hemoglobin, associated with high blood pressure. As determinations of the blood volume and plasma volume were not made, it is not known whether relative or absolute forms of polycythemia were present. This syndrome has been designated as polycythemia hypertonica, or Geisböck's disease. A careful perusal of Geisböck's cases does not lead one to believe that they represent a clinical entity. In the original paper of Keith, Rowntree, and Geraghty Case 18 represents a form of apparent polycythemia without hypertension. There was a normal volume of blood and a decreased volume of plasma with a high erythrocyte count.

The present series includes three cases apparently corresponding to the type of case described by Geisböck. One case was that of a man aged twenty-four years whose left kidney was functionless, due to hydronephrosis. The systolic blood pressure was 192 and the diastolic, 130. The erythrocytes numbered 6,150,000 for each cubic millimeter, and the percentage of cells by the hematocrit was 52. The hemoglobin was 19.2 gm. for each 100 c.c. of blood. The blood volume and plasma volume were respectively 82 c.c. and 48 c.c., for each kilogram of body weight. The viscosity was 7.1. The spleen was not palpable. This is an instance of polycythemic hypovolemia. Another

case was that of a woman aged forty-two years whose major complaint related to severe hypertension (systolic pressure 230 and diastolic 114). Because of cyanosis, the case was studied from the standpoint of possible polycythemia vera. The blood volume was 110 c.c. and the plasma volume 45 c.c. for each kilogram of body weight. The erythrocyte count was 7,360,000 for each cubic millimeter and the hemoglobin was 20.8 gm. for each 100 c.c. The viscosity was 8. The percentage of cells by the hematocrit was 59. The spleen was not palpable. The volume status was that of polycythemic hypervolemia. The third case was that of a man aged fifty-two years, who came to the Clinic complaining of burning paresthesia of the feet. The blood pressure was normal. Because the skin of the face and the mucous membranes of the mouth were very red, volume studies were made. The blood volume was 75 c.c. and the plasma volume, 34 c.c. for each kilogram of body weight. The patient was about 10 pounds overweight. The erythrocytes numbered 6,480,000 for each cubic millimeter, and there were 17.9 gm. of hemoglobin for each 100 c.c. of blood. The percentage of cells by the hematocrit was 54. There was a history of arsenical neuritis and the neurologic signs were those of peripheral neuritis in the lower extremities. The viscosity of the blood was 6.6. The retinal veins were not distended. The systolic blood pressure was 150 and the diastolic 100. The spleen was not palpable. This represents another instance of polycythemic hypervolemia.

We are in doubt as to the exact condition in these cases. In the two cases with high blood pressure we would infer the coexistence of two independent diseases; there is no evidence that the hypertension plays a causative rôle in the production of polycythemia. In the second case there was an absolute increase in the cell volume with a diminished volume of plasma and an increase in the number of erythrocytes for each cubic

millimeter. In the other two cases, both the blood volume and the plasma volume relative to body weight were decreased. It is also clear that hypertension may be absent, as in the third case and in the case reported by Keith, Rowntree, and Geraghty. Peacock studied the blood pressure in relation to the blood volume in this series of cases of polycythemia vera. In approximately 16 per cent of the cases there were increases in systolic and diastolic pressure above the levels for the ages of the patients. Reduction of blood volume and blood viscosity following treatment was not accompanied by a comparable reduction in the pressure. Furthermore, normal rather than increased blood volume and plasma volume are found in uncomplicated cases of essential hypertension; likewise, normal values for the number of erythrocytes and percentages of hemoglobin are the rule.

Parkes-Weber believes that polycythemia hypertonica is not a rare syndrome and that it occurs chiefly in middle-aged men. He separated this condition from polycythemia vera by the absence of an enlarged spleen and of marked facial cyanosis. He is of the opinion that the condition represents an episode during the course of hypertension. A secondary blood reaction develops, in the form of polycythemia, which delays or mitigates the harmful effects of the hypertension. The polycythemia disappears after a time, and the hypertension persists.

Seyderhelm and Lampe discussed this condition and maintained that the increase in the number of erythrocytes is relative, that the volume of the individual cell is small, and that the volume of the blood and of the cells is not increased. From the lack of volume studies in the reported cases it is impossible to draw conclusions as to the basis of the apparent polycythemia. We are inclined to believe that many of the cases reported in the literature of patients with enlarged spleens and hyper-

tension represent examples of a combination of polycythemia and essential hypertension. That the syndrome, polycythemia hypertonica, represents a disease entity is most unlikely.

LEUKEMIA (TABLES 20 AND 21)

Of four patients with myelogenous leukemia, volume of blood according to body weight was increased in all and in two it was definitely high. To enhance the evidence and to include a larger series, six cases reported by Keith⁶² are included. The mean for both groups was 109 c.c. for each kilogram or 3,840 for each square meter. The extremes varied from 92 to 131 c.c. for each kilogram of body weight and from 3,290 to 4,630 for each square meter of body surface. The plasma volume was 60 c.c. or more for each kilogram of body weight in all the cases. The mean value was 69 c.c. for each kilogram of body weight or 2,400 c.c. for each square meter of body surface. The mean value for cell volume was 40 c.c. for each kilogram of body weight, 3.5 c.c. (9.6 per cent) higher than the mean value for normal persons. The mean hemoglobin value was 11.1 gm. for each 100 c.c. of blood, representing mild anemia. The mean value for cells by the hematocrit was 36.6 per cent.

The average volume of blood for Keith's six cases of myelogenous leukemia was 110 c.c. and the average plasma volume was 68 c.c. for each kilogram of body weight. The average values for the four cases in our group and the six cases in Keith's group were comparable. The mean values for both groups are definitely high both for the blood volume and plasma volume, representing examples of substantially polycythemic hypervolemia. The increase in the blood volume is due to the presence of abnormal cells and increased plasma. Definite anemia was present in eight of the ten cases according to the hemoglobin values, but the percentage of cells by the hematocrit

TABLE 20
MYELOGENOUS LEUKEMIA

Case.	Weight, kg.	Hemoglobin, gm. in each 100 c.c.	Cells by hematocrit, per cent.	Blood.			Plasma.		
				Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	65	15.6	41	7,350	113	4,176	4,340	67	2,460
2	59	10.7	29	5,830	99	3,430	4,140	70	2,430
3	50	15.0	48	6,280	125	4,160	3,260	65	2,150
	45	11.1	34	5,300	117	3,680	3,500	78	2,430
	49		38	5,750	117	3,830	3,560	72	2,375
4	52	9.8	28	4,810	92	3,600	3,460	66	2,200
5*	64	7.8	22	6,400	100	3,520	5,000	77	2,740
6	51	14.2	41	5,670	111	3,930	3,340	65	2,320
7	51	11.1	43	5,360	105	3,550	3,050	60	2,050
8	68	11.1	37	7,270	107	4,010	4,580	67	2,530
9	56	7.2	26	5,370	96	3,290	3,970	70	2,420
10	53	7.4	47	6,945	131	4,630	3,680	69	2,500
Mean values . . .	57.7	11.1	36.6		109	3,840		69	2,400
Probable error	1.3	0.6	1.8		2.6	85		0.7	42

* Cases 5 to 10 have been reported by Keith.⁶²

was fairly high considering the anemia. This is due to the increased number of abnormal cells.

In two of four patients with lymphatic leukemia, blood volume definitely was increased. The average value was 98 c.c. for each kilogram of body weight and 3,570 c.c. for each

TABLE 21
LYMPHATIC LEUKEMIA

Case.	Weight, kg.	Hemoglobin, gm. in each 100 c.c.	Cells by hematocrit, per cent.	Blood.			Plasma.			Cells.	
				Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of surface area.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of surface area.	Total volume, c.c.	C.c. for each kg. of body weight.
1	56	12.3	43	5,100	90	3,270	2,910	51	1,870	2,190	39
2	61	13.6	40	6,990	114	4,060	4,190	68	2,440	2,800	46
3	71	13.7	38	6,200	87	3,500	3,840	54	2,180	2,360	33
4	55	11.8	42	5,590	102	3,440	3,290	57	2,020	2,300	42
Arith- metic values		12.8	40.7	5,970	98	3,570	3,560	57.5	2,120	2,412	41

square meter of body surface. The average value for the plasma volume was 57.5 c.c. for each kilogram of body weight and 2,120 c.c. for each square meter of body surface. The average cell volume according to body weight was about 4 c.c. (10.9 per cent) greater than the normal mean value. According to the hemoglobin determinations, mild grades of anemia were present in all cases.

COMMENT

The volume of blood in myelogenous leukemia is definitely high. The increase is due to both plasma and cells. The volume status is polycythemic hypervolemia. As will be noted, there was considerable variation for the volume of the cells in these cases. The percentage of cells by the hematocrit varied from 22 to 48. In five instances, Cases 1, 3, 6, 7 and 10, the hematocrit values were normal or increased. In these, the blood volume for each kilogram of body weight was high. It is interesting to

note that frequently, in the cases with a definitely high volume of blood, the plasma volumes also were increased proportionally. In contrast with this, we have found that in polycythemia vera, with the huge increase in the cell volume, the plasma volume is unchanged or only slightly increased. Anemia was present in eight of the ten cases. The increase in plasma volume stands in some relationship to the presence or degree of anemia, and in Case 3, in which repeated determinations of the blood volume were carried out, there was a drop in the hemoglobin and the percentage of cells by the hematocrit and in the total blood volume, with an increase in the amount of plasma for each kilogram of body weight and for each square meter of body surface.

In the few cases of lymphatic leukemia, the blood volume for each kilogram of body weight and for each square meter of body surface was lower than that obtained in the myelogenous types, but was significantly high when compared with the mean for normal persons. In two of the cases there was more than 100 c.c. of blood for each kilogram of body weight. The plasma volume was increased proportionately to the blood volume; for the group, therefore, the volume status was substantially simple hypervolemia. Anemia was present to a mild degree in all the cases. The average value by hematocrit was slightly decreased.

The explanation of the cause of the increased blood volume in leukemia has been studied by several workers. Keith⁶² carried out experiments in vitro with the blood of a patient with leukemia of the splenic type to determine whether the abnormal leukocytes took up appreciable amounts of dye. Evidence was not found to show that this occurred. We were interested in determining whether the dye disappeared from the circulation more rapidly in cases of leukemia, thus making it appear that the blood volume and plasma volume were in-

creased. Mixing curves were determined after three-minute, four-minute, and six-minute periods in two cases. The rate of disappearance of the dye was found to be approximately the same as that for the normal controls. Further explanation for the increased blood volume and plasma volume may be related to the splenomegaly which is present in this condition. As will be shown and discussed in Chapter IX, cases of splenomegaly with and without anemia are usually accompanied by an increase in the blood volume and plasma volume.

Greppi, using the dye method in three cases of leukemia, found that the blood volume was increased, averaging 130 c.c. for each kilogram of body weight, and that the plasma volume was increased, averaging 72 c.c. for each kilogram. He believed that the tendency to a large plasma volume is not uniform in all cases of splenomegaly, emphasizing the slight or negligible increase which occurs in polycythemia vera. He raised the question whether splenic reticulo-endothelial cells may remove an abnormal amount of dye from the circulation. Our studies *in vivo* and *in vitro* seem to show that there is no evidence that the dye disappears from the circulation any more rapidly in cases of leukemia or other forms of splenomegaly than from the circulation of normal subjects.

The values for the blood volume in chronic leukemia obtained by other workers, using different methods, show wide differences. Plesch and Oerum,⁸⁴ using the method of infusion with physiologic sodium chloride solution, found normal values for the blood volume in one case. Von Behring, using the same method, found fairly high total blood volume.

SUMMARY

In chronic secondary anemia there is a reduction in the volume of the blood and of the cells according to body weight and body surface. The mean values for the plasma volume ac-

cording to body weight are somewhat increased. Rarely definitely high total plasma volume exists. The plasma replacement factor for this group is 42 per cent. The volume status according to the mean value is oligocythemic hypovolemia.

In primary anemia there is a similar reduction in the blood volume and cell volume. The plasma volume relative to body weight and body surface is higher and the cell volume much lower than in secondary anemia. The plasma replacement factor of 30 per cent is less than that obtained in the group of cases of secondary anemia. According to the mean value, the volume status is oligocythemic hypovolemia.

The absolute blood volume and the volume relative to body weight and body surface are markedly increased in polycythemia vera. The mean value for the plasma volume according to body weight is increased. The volume status is polycythemic hypervolemia. The increase in the blood volume is due chiefly to the absolute increase in the number of erythrocytes. This increase in the cell volume constitutes, we believe, a basic disturbance in this disease, one on which many of the symptoms and signs depend.

Chronic leukemia of the myelogenous type is accompanied by increased volume of blood according to the body weight and body surface. The mean values for plasma volume relative to body weight and body surface are high. In cases without anemia or with questionable anemia the blood volume was higher than in the cases with anemia, but plasma volume was higher according to body weight and body surface in the cases with anemia. The volume status was polycythemic hypervolemia.

In chronic leukemia of the lymphatic type, the average values for blood volume and plasma volume, in proportion to body weight and body surface, are increased with a slight increase in the cell volume. The volume status was polycy-

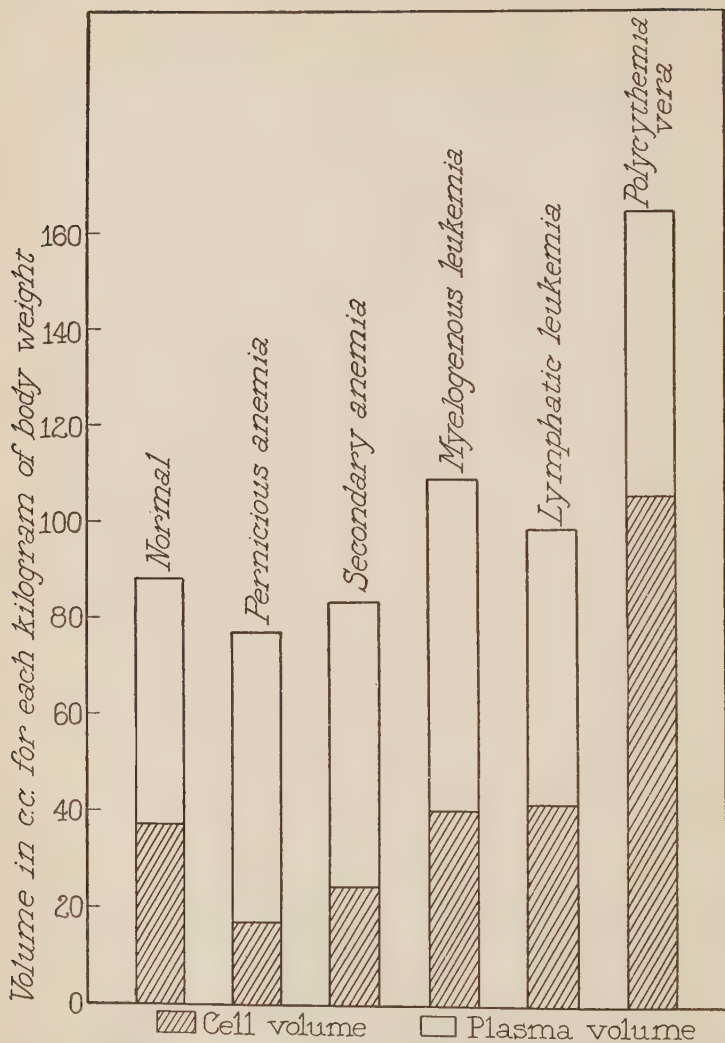


FIG. 12.—Graphic representation of mean values for volume of blood, plasma, and cells in normal conditions and in various diseases.

themic hypervolemia for the group. Slight anemia, according to the hemoglobin values, was present in all cases; the hematocrit values for cells were normal. This is explained by the increased number of leukocytes. Figure 12 shows the mean values for blood, plasma, and cells in various diseases of the blood.

Chapter IX

DISEASES OF THE SPLEEN AND LIVER

Thirty-four cases representing different forms of splenomegaly have been studied by Giffin and Brown to determine the volume of the blood and plasma in cases of splenomegaly, the effects of splenectomy on the blood volume, and whether or not the anemia when present is apparent or actual. We have added to their group nine cases of cirrhosis of the liver with splenomegaly and ascites and five cases of splenomegaly of the infectious type. Clinically, the forms were classified as follows: (1) Primary splenomegaly without anemia, six cases; (2) cirrhosis of the liver with splenomegaly, nine cases; (3) hemolytic jaundice, eleven cases; (4) primary splenomegaly with anemia, eighteen cases, and (5) chronic infectious splenomegaly and miscellaneous diseases, five cases.

PRIMARY SPLENOMEGALY WITHOUT ANEMIA (TABLE 22)

These cases were considered examples of primary splenomegaly since none was included in which known etiologic factors, such as syphilis, antecedent infection, and various blood dyscrasias were present. The mean body weight of the patients was 65.8 kg. The hemoglobin and erythrocyte values were normal. The mean value for hemoglobin was 14.5 gm. per cent. The mean value for cells by the hematocrit was 41.6 per cent and for erythrocytes 4,580,000. The mean blood volume for each kilogram of body weight was 102.5 c.c.; according to body surface for each square meter, the mean value for blood volume was 3,750 c.c. In four of the six cases, the blood

TABLE 22
SPLENOMEGALY WITHOUT ANEMIA

Case.	Age.	Sex.	Surface area, sq. m.	Weight, kg.	Hemoglobin, gm. in each 100 c.c.	Erythrocytes, in each cu. mm., millions.	Cells by hematocrit, per cent.	Blood.			Plasma.			Weight of spleen, gm.
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	49	M.	1.83	76	13.9	4.66	42	7,480	98	4,090	4,340	57	2,370	
2	25	M.	1.74	60	15.6	5.10	41	6,330	105	3,750	3,740	62	2,210	920
3	36	M.	1.70	58	15.4	5.24	45	6,290	108	3,700	3,460	60	2,040	
4	26	F.	1.68	60	15.4	3.88	43	6,390	106	3,800	3,640	60	2,170	800
5	43	M.	1.68	62	15.6	3.82	38	5,520	89	3,260	3,430	55	2,040	720
6	42	M.	1.83	70	11.0	4.57	39	7,390	105	4,040	4,500	64	2,460	464
Mean values....			1.75	65.8	14.5	4.58	41.6		102.5	3,750		60	2,217	
Probable error..			0.01	1.89	0.421	0.17	0.642		2.1	76.1		0.7	41.1	

volume was more than 100 c.c. for each kilogram, the upper limit of normal (footnote, page 54). The plasma volume, according to body weight, ranged from 55 to 64 c.c. for each kilogram, and according to body surface, from 2,040 to 2,460 c.c. for each square meter. The mean values for plasma were 60 c.c. for each kilogram and 2,217 c.c. for each square meter. In four of the six cases the plasma volume was 60 c.c. or more.

The volume status, according to the mean values in this group, was substantially that of simple hypervolemia. The normal ratio of cell volume to plasma volume was preserved. There was simply a larger amount of normal blood, such as has been noted in cases of chronic passive congestion and in cases of arteriovenous fistula, conditions in which larger amounts of blood seem to be necessary to maintain circulatory efficiency.

The spleen was removed in four cases. The weights are shown in Table 22. In those cases in which the volume studies were carried out at short intervals after splenectomy, normal

values were found. In those cases in which the longer intervals of one year and four years elapsed between splenectomy and volume studies, simple hypervolemia was found.

CIRRHOSIS OF THE LIVER WITH SPLENOMEGALY (TABLE 23)

In the nine cases of cirrhosis of the liver of the portal type, with enlargement of the spleen, the blood volume was determined during the period of maximal ascites. In all cases the liver was small and the collateral circulation well developed. In Case 2 splenectomy was performed. The weight of the spleen is shown.

TABLE 23

CIRRHOSIS OF THE LIVER WITH SPLENOMEGALY

Case.	Age.	Sex.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by the hematocrit, per cent.	Blood.			Plasma.			Comment.
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	43	M.	60	8.6	27	6,320	105	3,780	4,615	77	2,760	Ascites graded 3.
2	43	F.	43	13.9	33	3,750	87	2,620	2,515	58	1,760	Weight of spleen, 450 gm.
3	70	M.	83	14.0	38	8,190	99	4,240	5,075	61	2,625	Ascites graded 3.
4	55	M.	73	12.7	34	7,090	97	3,870	4,675	64	2,550	Ascites graded 2.
5	30	F.	55	12.3	34	6,060	110	3,785	4,000	73	2,500	Ascites graded 3.
6	41	F.	57	13.7	35	6,090	107	3,855	3,955	69	2,500	
7	57	M.	80	15.1	40	6,995	87	3,600	4,185	52	2,155	Ascites graded 3.
8	36	M.	65	14.4	39	5,795	89	3,320	3,530	54	2,020	Ascites graded 2.
9	50	M.	65	10.9	34	8,400	129	4,660	5,540	85	3,080	Ascites graded 2.
Mean values . .			65	14.2	35.4		101.4	3,767		65.8	2,450	
Probable error.			2.7	0.46	0.87		2.8	120		2.48	84.2	

The mean value for hemoglobin was 14.2 gm. in each 100 c.c. for the actual hemoglobin, 14.0 gm. for each kilogram of

body weight, or 534 gm. for each square meter of body surface.

The mean value for the cells by the hematocrit was 35.4 per cent. The range of blood volume was from 87 to 129 c.c., with a mean of 101.4 c.c., for each kilogram of body weight; and 2,620 to 4,660 c.c., with a mean of 3,767 c.c., for each square meter of body surface. In four cases (44 per cent) the blood volume for each kilogram of body weight was 100 c.c. or more. The range of plasma volume was from 52 to 85 c.c. for each kilogram, or 1,760 to 3,080 c.c. for each square meter. The mean value for plasma was 65.8 c.c. according to body weight, approximately 15 c.c. higher than the mean value for normal persons, and 2,450 c.c. according to body surface. In six cases (66 per cent) the plasma volume was 61 c.c. or more for each kilogram.

According to concentration values, mild grades of anemia were present in six of the nine cases, but when the circulatory hemoglobin was calculated according to body weight and body surface true mild anemia was found to be present in four cases. The volume status according to the mean values was that of oligocythemic hypervolemia. The increase in volume is due to plasma. These data apparently would show that true dilution was present in several cases.* The degree of actual anemia was too slight to warrant the belief that the loss of cells was primary and that the increase in plasma was a replacement phenomenon.

* Dilution producing apparent anemia is present when the blood volume and plasma volume are not decreased proportionately with decrease in cell volume. Usually the loss of hemoglobin and cells is followed by an increase in plasma so that degrees of dilution exist with actual anemia. Examples of pure dilution anemia, in which the amount of fluid is increased and the cell volume remains constant, are not common in our experience. Probably the condition exists in some of the cases of cirrhosis of the liver, since the volume of hemoglobin according to body weight and body surface is within the range for normal persons. But the increased blood volume and plasma volume give a reduced amount of hemoglobin for each 100 c.c. of blood.

HEMOLYTIC JAUNDICE (TABLE 24)

The clinical features in the eleven cases in this group were characteristic of this disease. The spleen was enlarged (graded 1 to 3) in each case. Splenectomy was performed in ten cases. The weight of the spleen varied from 203 to 1,640 gm.; the mean value was 950 gm. The ages varied from four to fifty-

TABLE 24
HEMOLYTIC JAUNDICE

Case.	Age.	Sex.	Body surface, sq. m.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes, in each cu. mm., millions.	Cells by hematocrit, per cent.	Blood.			Plasma.			Weight of spleen, gm.
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	57	F.	1.45	45	8.1	2.33	18	4,480	100	3,090	3,680	82	2,540	800
2	31	M.	1.87	67	12.4	3.54	28	4,950	74	2,650	3,560	53	1,900	1,450
3	35	F.	1.50	50	8.6	3.60	23	4,350	87	2,900	3,360	67	2,240	820
4	43	F.	1.70	61	8.1	3.74	20	4,240	70	2,490	3,390	55	1,995	945
5	22	F.	1.46	52	6.7	3.02	20	4,320	83	2,940	3,450	66	2,350	1,640
6	6.5	F.	0.83	20	8.3	2.84	19	3,060	153	3,690	2,470	123	2,975	500
7	4	F.	0.77	18	8.9	3.69	24	1,560	87	2,025	1,190	66	1,545	203
8	9	M.	1.00	23	6.8	2.57	16	2,050	89	2,050	1,720	75	1,720	550
9	22	F.	1.60	54	7.7	2.24	24	5,210	97	3,250	3,960	73	2,475	
10	14	M.	1.16	32	10.3	3.65	20	2,670	83	2,300	2,140	67	1,860	784
11	27	M.	1.60	54	11.4	2.93	25	4,950	92	3,090	3,710	69	2,320	1,500
Mean values..			1.38	42.8	8.8	3.10	22.3		93.2	2,791		73.1	2,200	950
Probable error.			0.72	3.37	0.37	0.109	0.67		0.91	98.5		3.15	79.3	97

seven years. Three patients were aged less than ten years. The mean body weight was 42.8 kg. and the mean body surface 1.38 sq. m. Determinations of blood volume were made one or two days preceding operation, and from nine to seventeen days afterward.

The mean blood volume was 93.2 c.c. for each kilogram of body weight and the range was from 70 to 153 c.c. For each square meter the blood volume was 2,791 c.c. The plasma volume varied from 53 to 123 c.c. with a mean value of 73.1 c.c. for each kilogram or 2,200 c.c. for each square meter. In 82 per cent of the cases, plasma volume was more than 60 c.c. for each kilogram. Actual anemia was present in all the cases, as shown by the volume of hemoglobin for each kilogram of body weight and for each square meter of body surface. The mean value for hemoglobin was 8.8 gm. per cent; for the circulating hemoglobin 8.1 gm. for each kilogram of body weight. The mean value for the cells by the hematocrit was 22.3 per cent.

The volume status in the cases of hemolytic jaundice was that of mild hypervolemia of the oligocythemic type,* a slightly increased blood volume with a markedly decreased ratio of the cell volume to the plasma volume. The plasma volume is about 22 c.c. greater for each kilogram as compared to the mean for normal persons, an excessively high value. The high incidence of increased volume of plasma seems to be related to the anemia and to the enlarged spleen. The anemia present was actual according to the values for the hemoglobin calculated according to body weight and body surface.

The replacement index in the cases of hemolytic jaundice was 95 per cent calculated as follows: a mean value for cell volume of 20.1 c.c. for each kilogram is a decrease of approximately 16.4 c.c. or 45 per cent as compared with the mean value for normal persons of 36.5 c.c. The plasma volume increased approximately 22 c.c., as compared with the mean value for normal persons of 51.2 c.c.; this is an increase of 42.7 per cent.

* The inclusion of Case 6 (Table 24), that of an emaciated girl aged six and a half years, with a blood volume of 153 c.c. for each kilogram of body weight, materially increased the mean value. Without this abnormal quantity the mean value is slightly less than the mean for normal persons.

The replacement index was 42.7 divided by 45 (95 per cent). This is a high index as compared with that found in cases of primary and chronic anemia.

Volume determinations were made in nine cases from nine to seventeen days after operation. The actual cell volume was

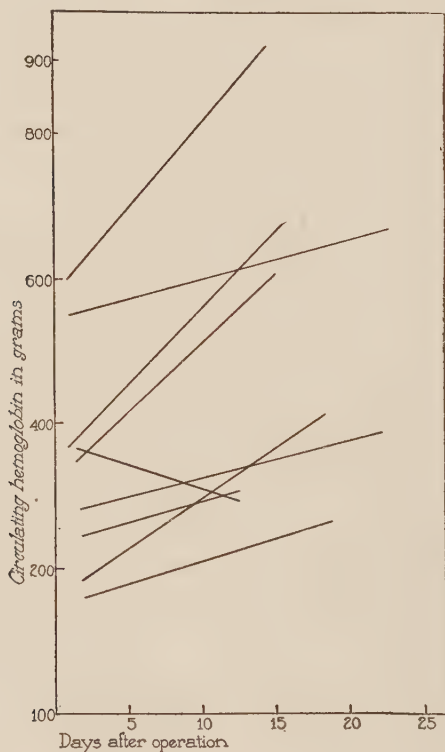


FIG. 13.—Curves showing in grams the changes in the total volume of hemoglobin following splenectomy in cases of hemolytic jaundice.

increased markedly in all but one case; the average was 666 c.c. The blood volume increased in five cases, decreased in two cases, and was unchanged in two cases. The plasma volume

increased in five cases and decreased in four cases. The hemoglobin volume increased in all but one case (Fig. 13); the average total increase was 183 gm. These changes in the volume of hemoglobin following operation were also reflected in the concentration values for the erythrocytes and hemoglobin, but in less degree, since volume variations in plasma were present. A definite correlation of blood volume and plasma volume with the weight of the spleen could not be demonstrated.

PRIMARY SPLENOMEGALY WITH ANEMIA OR BANTI'S DISEASE
(TABLE 25)

Definite grades of anemia, according to the relative standards for hemoglobin and erythrocytes, were present in each of the eighteen cases. The mean value for body weight was 64.2 kg., and for weight of the spleen 1,128 gm. The mean value for hemoglobin was 9.8 gm. per cent, 9.7 gm. for each kilogram of body weight, and 355.6 gm. for each square meter of body surface. The mean value for erythrocytes was 3,700,000 for each cubic millimeter, and the mean value for cells by the hematocrit 30.3 per cent. The blood volume varied from 67 to 113 c.c. for each kilogram of body weight; the mean value was 97.5 c.c., and in ten of the cases (55 per cent) it was more than 100 c.c. For each square meter of body surface the range of blood volume was 2,620 to 4,440 c.c., with a mean value of 3,600 c.c. The plasma volume ranged from 50 to 83 c.c. for each kilogram of body weight; the mean value was 68.6 c.c., approximately 17 c.c. (33 per cent) higher than the normal. The plasma volume ranged from 1,810 to 3,270 c.c. for each square meter of body surface; the mean value was 2,512 c.c. Plasma volume relative to body weight in excess of 60 c.c. for each kilogram (upper range of normal) was found in 83 per cent of the cases in this group.

TABLE 25

PRIMARY SPLENOMEGALY WITH ANEMIA

Case.	Age.	Sex.	Body surface, sq. m.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes, in each cu. mm., millions.	Cells by hematocrit, per cent.	Blood.			Plasma.			Total weight of spleen, gm.
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	43	F.	1.60	53	11.8	3.50	29	5,780	109	3,610	4,100	77	2,560	
2	41	M.	1.96	74	8.3	4.34	30	8,300	112	4,230	5,800	78	2,960	300
3	31	F.	1.77	69	7.6	3.50	26	4,630	67	2,620	3,430	50	1,940	400
4	47	M.	1.93	80	9.2	3.33	26	8,510	107	4,410	6,320	79	3,270	1,460
5	23	F.	1.30	44	8.5	3.43	32	4,720	107	3,630	3,210	73	2,470	700
6	30	M.	2.02	87	10.9	3.96	29	7,460	86	3,690	5,300	61	2,630	1,440
7	35	M.	1.87	72	7.9	4.32	30	7,350	102	3,910	5,140	71	2,750	1,160
8	28	F.	1.65	62	11.6	4.29	34	6,380	103	3,870	4,210	68	2,550	1,140
9	29	F.	1.46	49	7.6	3.18	25	4,750	97	3,250	3,560	73	2,440	1,000
10	34	F.	1.65	59	12.8	4.04	42	6,400	108	3,850	3,710	63	2,240	986
11	40	F.	1.62	56	11.1	3.69	37	5,860	104	3,620	3,690	66	2,270	1,000
12	42	F.	1.59	53	12.0	3.96	32	6,010	113	3,780	4,090	77	2,570	
13	49	M.	2.00	85	5.6	2.71	21	7,120	84	3,560	5,620	66	2,800	800
14	50	M.	1.76	70	7.5	2.79	23	6,500	93	3,700	5,000	71	2,840	1,480
15	18	F.	1.65	60	10.0	3.86	31	5,930	99	3,590	4,090	68	2,480	1,800
16	55	F.	1.49	54	14.1	3.62	33	4,030	75	2,710	2,700	50	1,810	
17	59	F.	1.49	51	8.1	3.41	26	5,750	112	3,860	4,250	83	2,840	
18	26	M.	1.92	73	11.2	3.68	32	5,760	79	3,000	3,920	53	2,040	1,170
Mean values.			1.72	64.2	9.8	3.70	30.3	6,194.5	97.5	3,600	4,888	68.6	2,512	1,128
Probable error.....			0.03	2.1	0.4	0.7	0.8	189	2.1	70	152	1.4	57.3	

The mean values indicate increased volume of blood according to weight and body surface. The cell volume is reduced. The volume status was oligocythemic hypervolemia. The increase is due to the large amount of plasma. The anemia is of the actual type, but a degree of dilution is present and the

plasma volume more than replaces the loss in cells. The replacement index, when calculated for the mean values, is 191 per cent. If the increased amount of plasma is assumed to be due to loss of cells, this amount of replacement is almost complete. Giffin and Brown believe that the increase in plasma is not due entirely to the loss of cells as a compensatory effect of anemia, but that it precedes the development of anemia and may be related to circulatory needs for larger volumes. They base their conclusions on the increased blood volumes found in cases of primary splenomegaly without anemia.

The spleen was removed in fourteen of the eighteen cases and in seven cases volume was estimated before and after splenectomy. Two weeks after operation there was an average decrease in blood volume of 462 c.c. (7.4 per cent). The average decrease in the plasma volume was 857 c.c. (17.5 per cent); variation in the blood volume and plasma volume was not uniform after splenectomy. The cell volume and hemoglobin volume were decreased in most cases. A slight increase was noted in one case.

CHRONIC INFECTIOUS SPLENOMEGALY AND MISCELLANEOUS DISEASES

The five cases in this group were separated from the cases of splenic anemia on the basis of antecedent history of sepsis and also on the basis of their less favorable response to splenectomy. The degree of splenic enlargement was not marked.

The average value for the volume of blood was 89 c.c. for each kilogram or 3,140 c.c. for each square meter of body surface. The average plasma volume was 59 c.c. for each kilogram of body weight and 2,119 c.c. for each square meter of body surface. Definite anemia according to concentration values was present in each case. In only one case was the plasma volume markedly increased.

It is apparent that the large plasma volume and the degrees of splenic enlargement that were noted in splenic anemia were not seen in this group of cases in which there were mild grades of splenomegaly. This is noteworthy, in view of the fact that definite clinical anemia was present in each case. Apparently the size of the spleen stands in some relationship to the increase in the plasma, as noted in the cases of primary splenomegaly with anemia.

COMMENT ON ALL GROUPS IN CHAPTER IX

The volume studies carried out in cases of splenomegaly have shown certain variations from the normal (Fig. 14) the most significant of which is the increase of plasma on the basis of body weight and surface area. This increase is no doubt actual. It cannot be ascribed to defects in the method. Carefully controlled studies were made on the rate of disappearance of the dye from the blood in five cases of splenic anemia to see if the rate of disappearance of dye from the blood was so fast as to give a spurious impression that the dye was being diluted by an increased amount of blood plasma. However, an increased rate of elimination could not be demonstrated. None of the dye appeared in the urine within a ten-minute period. The increased volume of plasma remaining after removal of the spleen apparently ruled out the argument that the dye is removed at an abnormal rate from the circulation by the reticulo-endothelial cells of this organ.

Further evidence on this point has been obtained by the following experiment. The blood volume of two patients with hemolytic jaundice was determined while they were on the operating table, just prior to the removal of the spleen. Twenty to thirty minutes after the injection of the dye, samples of blood were taken from the splenic artery, splenic vein, and splenic pulp. It was found that the concentration of the dye in

the three samples was exactly the same. These experiments seem to demonstrate conclusively that appreciable amounts of

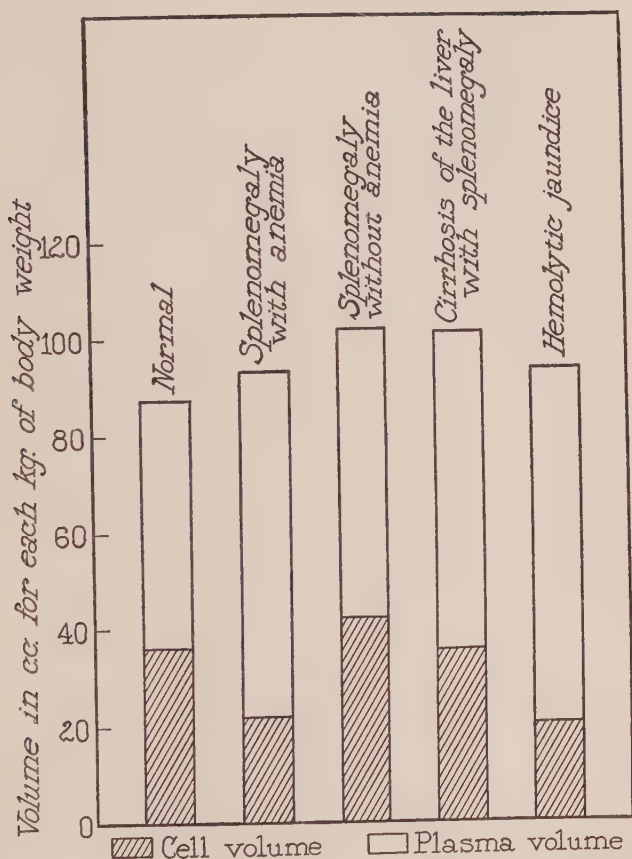


FIG. 14.—Graphic representation of mean values for volume of blood, plasma, and cells in normal conditions and in various diseases.

the dye are not taken up by the cells of the spleen in this type of case.

The increased volume of plasma apparently is closely re-

lated to the size of the spleen* in cases of splenomegaly with anemia (Fig. 15). This was less decisive in the cases of hemolytic jaundice. The explanation of this augmentation of plasma is not clear. The group of cases of splenomegaly without anemia, with increased volume of blood, is of particular interest in that it could be assumed that the subsequent developments

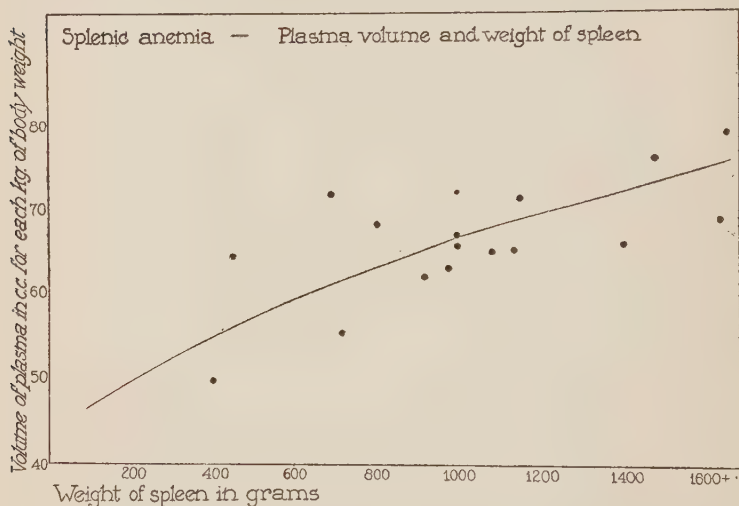


FIG. 15.—Curve showing correlation between plasma volume and weight of the spleen in primary splenomegaly with anemia.

could be either those of polycythemia or of anemia. Proof of the assumption that cases of splenomegaly without anemia might develop into cases of polycythemia does not exist, but evolution of cases of splenomegaly without anemia into typical examples of primary splenomegaly with anemia has been observed.

* In view of the recent work of Barcroft on the blood-storing function of the spleen, its contraction, and expression of erythrocytes from it, under various stimuli, we believe that further studies should be undertaken in the attempt to correlate changes in the volume of the blood with changes in the volume of the spleen.

It would appear that there is a pre-anemic stage in certain types of splenomegaly with anemia and in which there is an increased volume of blood. It is possible that this is induced to meet a circulatory need secondary to an enlarged abdominal vascular bed. With the loss of cells and the presence of anemia, an enlarged circulatory volume, composed largely of plasma, is maintained. This explanation seems more reasonable than the assumption that the increased amount of plasma is a replacement process secondary to loss of cell volume. The excessively high replacement indexes obtained in these cases is against the latter theory. An additional argument against the replacement theory rests on the fact that, in hemolytic jaundice, a constant plasma volume is maintained or that there is even an increase in the plasma volume following splenectomy as well as a decisive improvement in the anemia.

This study has shown that in cases of splenomegaly with anemia, and of hemolytic jaundice, the anemia shown by the concentration values is actual, although it is accentuated by dilution. In the cases of cirrhosis of the liver, the anemia in several cases probably is due entirely to dilution. The hypervolemia in these cases appears similar to the moderate increases in the volume of blood observed in certain other forms of circulatory disturbance.

The effects of splenectomy, as studied by the volume determinations, are confirmatory of the curative effects of this procedure in hemolytic jaundice. The regeneration of erythrocytes and hemoglobin is most striking, and constitutes actual and not apparent increases in these constituents.

In the cases of splenomegaly with anemia, removal of the spleen is less effective. Actual increases in the cell volume and hemoglobin volume did not occur within the period of observation. A decrease in the blood volume and plasma volume was the rule.

Chapter X

VARIOUS TYPES OF EDEMA*

In thirty-five cases of edema one or more determinations were made of the blood volume and plasma volume. The cases were divided into the following clinical groups: acute and sub-acute glomerulonephritis, twelve cases; nephrosis, nine cases; cardiac edema, eleven cases, and diabetic edema, three cases. The diagnoses in the first group were made independently by the various attending clinicians, following the classification of Volhard. The volume studies were made soon after the patient's admission to the hospital, during the period of maximal edema. However, the blood volume and plasma volume were calculated on the basis of the body weight following the disappearance of the edema, subsequently designated here as the corrected body weight.†

GLOMERULONEPHRITIS (TABLES 26, 27, AND 28)

The mean blood volume in twelve cases of glomerulonephritis with edema was 75.4 c.c. for each kilogram of corrected (edema-free) body weight, or 2,650 c.c. for each square meter of body surface. The range was from 59 to 105 c.c. for each kilogram of body weight. The mean value for the plasma volume was 52.5 c.c. for each kilogram of corrected body weight and 1,875 c.c. for each square meter of body surface. The range was

* The term "edema," as used here, indicates palpable edema and not pre-edematous states as revealed by the elastometer or salt absorption tests.

† The value for the corrected body weight is subject to a degree of error which cannot be estimated.

from 38 to 70 c.c. for each kilogram. The mean value for hemoglobin was 11.2 gm. per cent, 8.3 gm. for each kilogram, and 300 gm. for each square meter. Actual anemia was present in every case but one (Case 10). The percentage of cells as determined by the hematocrit varied from 11 to 41. The mean was 30 per cent. The mean value for cell volume was 27 c.c. for each kilogram, and 800 c.c. for each square meter. If correction is not made for the weight of the edema fluid, lower values are obtained for the blood volume and plasma volume relative to body weight, depending obviously on the amount of edema fluid in the tissues and serous cavities.

In eight of the twelve patients (Table 27) repeated determinations were made during the period of diuresis. The treatment consisted of allowing only a low fluid and low salt intake. Paracentesis was performed in several cases. In one case the high protein diet and desiccated thyroid did not produce striking results. It is evident that the decrease in the volume of blood, which usually occurs during the period of diuresis, was noted in six of the eight cases. This decrease is due to a lessening in both the plasma volume and the cell volume. The sum of these changes is reflected in the total blood volume. In Cases 1 and 2 there was a loss in the volume of the plasma, but the change in the cell volume was not significant. In Case 3 there was a slight or negligible decrease in the plasma volume and the cell volume showed a sharp decrease. In Case 5 both factors were at play, a sharp loss occurring in both plasma and cells. In Case 6 there was a moderate increase in the plasma and an insignificant decrease in cells. In Case 9 there was a decrease of 960 c.c. in the plasma volume and the decrease in cells was insignificant. Significant change was not noted in Case 10. In Case 12 there was a considerable decrease in the cell volume and a slight increase in plasma volume.

TABLE 26.—GLOMERULONEPHRITIS WITH EDEMA

Case.	Age.	Sex.	Body weight, kg.	Edema, grade.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Cells.			Hemoglobin.			Comment.
							Total volume, c.c.	C.c. for each kg. of corrected body weight.*	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	Total volume, gm.	Gm. for each kg. of corrected body weight.	Gm. for each sq. m. of body surface.	
1	22	M.	60	3+	11.5	28	4,900	81	2,970	3,530	59	2,190	1,370	22	823.1	564.0	9.4	341.8	Marked edema; ascites.
2	21	M.	64	3	11.3	24	4,050	63	2,350	3,080	48	1,780	970	15	560.0	458.0	7.2	266.0	Generalized edema; ascites.
3	17	F.	65	3+	12.3	36	5,210	80	2,910	3,330	51	1,860	1,880	28	1,050.0	640.8	9.8	357.9	Uremia; pulmonary edema.
4	15	M.	51	4	10.7	31	3,620	70	2,380	2,500	48	1,645	1,120	22	736.8	387.3	7.6	254.8	Ascites; marked edema.
5	46	M.	80	2+	11.3	27	4,740	59	2,370	3,460	43	1,730	1,280	16	648.0	535.6	6.7	241.2	Progressive edema and anemia.
6	25	F.	48	3+	11.0	25	3,050	63	2,130	2,280	48	1,600	770	16	531.5	335.5	7.0	229.9	Ascites with generalized edema.
7	16	F.	66	3	11.3	35	3,900	59	2,050	2,540	38	1,370	1,360	21	735.0	440.7	6.7	238.0	Acute "flare-up" of chronic glomerulonephritis.
8	20	M.	60	1-	13.3	31	4,540	75	2,680	3,130	52	1,850	1,410	22	834.0	603.8	10.0	357.0	Acute nephritis.
9	17	M.	56	2	5.5	11	4,050	72	2,440	3,600	64	2,150	450	8	272.7	222.7	3.9	134.9	Subacute nephritis; mastoiditis.
10	20	M.	75	2	15.6	41	7,010	93	3,700	4,140	55	2,190	2,870	38	1,518.0	1,093.5	14.6	579.0	Acute nephritis, one month's duration.
11	20	M.	61	2	9.4	28	4,580	75	2,760	3,300	54	1,990	1,280	21	770.0	430.5	7.0	259.2	Glomerulonephritis and nephrosis.
12	19	F.	46	3	9.7	33	4,830	105	3,400	3,240	70	2,280	1,590	35	1,120.0	468.5	10.1	329.9	Subacute nephritis and nephrosis.
Mean values			63		11.2	30		75.4	2,650		52.5	1,875		27	800		8.3	300.0	
Probable error.			1.99		0.45	0.44		2.76	95.4		1.73	49.8		1.33	60.5		0.56	20.9	

* The term "corrected body weight" refers to the weight after the disappearance of edema.

TABLE 27
DIURESIS IN GLOMERULONEPHRITIS

Case.	Weight loss, kg.	Change in cells by hematocrit, per cent.	Blood.		Plasma.		Duration of diuresis, days.
			Increase, c.c.	Decrease, c.c.	Increase, c.c.	Decrease, c.c.	
1	30	+ 2		580		500	63
2	27	- 5	40			160	34
3	2.5	- 9		940		170	14
5	8.5	-13		2,090		880	83
6	14	- 6	150		310		50
9	9	- 9		750		960	31
10	10			100			11
12	16	-13		585	150		27

Table 28 gives the results of repeated determinations in Case 5 carried out during a period of eighty-three days of treatment. There was only moderate loss of weight. The edema was fluctuating as shown by the variations in the body weight. During the period, the volume of the whole blood gradually decreased. This decrease was quite independent of the variations in the amount of edema and represented an actual loss of cells. The plasma volume was fairly stable during the first month. The later determinations of the volume of the plasma showed a gradual decrease following, roughly, the diminishing blood volume. The percentage of cells, as obtained by the hematocrit, revealed a gradual reduction. Thus progressive anemia was taking place during the period of observation.

The data in this group are comparable with those of our former studies²⁶ indicating that a normal or decreased volume of blood is found in glomerulonephritis with edema. On the basis of the condition of the blood, the cases of glomerulo-

TABLE 28

SUBACUTE GLOMERULONEPHRITIS WITH DEVELOPING ANEMIA AND INCOMPLETE DIURESIS*

Case.	Date, 1922.	Body weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.		Plasma.		Comment.
					Total volume, c.c.	C.c. for each kg. of corrected body weight.	Total volume, c.c.	C.c. for each kg. of corrected body weight.	
5	10/ 7	94	18.6	38	6,830	85	4,240	53	Marked edema, ascites.
	10/17	90	17.0	43	7,340	91	4,190	52	Some dye in urine.
	10/24	90	17.0	35	6,220	78	4,040	51	
	11/ 7	90	16.8	40	5,710	71	3,460	43	
	11/17	87	13.3	35	6,510	81	4,240	53	Paracentesisabdominis.
	11/29	86	13.1	37	6,720	84	4,240	53	
	12/ 7	90	13.8	28	4,910	61	3,830	48	
	12/13	89	12.8	27	4,740	59	3,460	43	
	12/23	90	10.9	28	5,210	65	3,750	47	
	12/30	86	9.6	29	4,740	59	3,360	42	Edema 2; ascites 1.

* The condition in this case first was diagnosed as nephrosis but, later, signs of progressive glomerulonephritis appeared.

nephritis with edema can be divided into two groups: those without anemia, and those with anemia. The first group comprises the more acute cases; the blood volume and plasma volume have normal values, with a normal ratio of cells to plasma (simple normovolemia). There is no evidence that dilution or edema of the blood, so-called hydremic plethora, exists. In the other group, comprising the subacute and more chronic forms, definite grades of true anemia are almost uniformly present. The blood volume is decreased, due to an absolute decrease in

the volume of cells, and the plasma volume is normal. The clinical manifestations of pallor of the skin and lowered specific gravity of the blood would seem to suggest that a dilution process of the blood was present, but our studies show that variations are due to changes in the volume and constituents of the blood common to the usual types of secondary anemia without edema. We are of the opinion that the changes occurring in the blood during the disappearance of edema are related largely to the further loss of cells and the consequent adjustments in the plasma.

The mean values for the blood volume are decreased in glomerulonephritis with edema according to corrected body weight. The mean values for the plasma volume according to body weight are essentially equivalent to the mean for normal persons. The cell volume is decreased. This represents true or actual anemia and constitutes an essential part of the disease. The volume status is oligocythemic hypovolemia. The volumes in this disease and in simple chronic anemia are comparable. Diuresis does not produce uniform changes in the volume of the blood and plasma. The changes observed during the period of diuresis are those related to the developing anemia. Replacement of the decreased cell volume by plasma is slight or negligible compared to that occurring in both primary and secondary chronic anemia without edema. If replacement does occur it is not adequate to maintain the blood volume at the level of the mean for normal persons.

NEPHROSIS (TABLES 29 AND 30)

In the nine cases in this group, determinations were made of the blood volume and plasma volume during the period of edema. This disease has been described as a clinical entity. It is characterized by high grades of edema and albuminuria and by a high globulin level, and a diminished protein content of the

TABLE 29
NEPHROSIS: STAGE OF EDEMA

Case.	Age.	Sex.	Grade of edema.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Comment.
						Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body weight.	
1	37	M.	2	17.6	45	6,680	89	3,630	3,670	49	2,000	Pure nephrosis.
2	33	M.	2	17.3	44	5,100	102*		2,860	57		Enaciated; amyloid degeneration of kidney.
3	25	M.	3	17.0	39	5,370	93	3,210	3,270	56	1,950	Generalized edema.
4	32	M.	2-3	12.3	30	5,780	103	3,450	4,050	71	2,420	Mixed lesion; glomerulonephritis.
5	31	F.	1+	12.5	33	4,850	101	3,210	3,240	68	2,150	Pure nephrosis.
6	19	M.	2+	12.6	24	6,010	105	3,780	4,510	79	2,840	Nephrosis and Pott's disease.
7	46	M.	4	16.4	38	6,830	85	3,450	4,240	53	2,140	Nephrosis, at this state, ascites graded 2.
8	25	F.	3+	11.6	39	4,660	103	3,480	2,840	64	2,120	Ascites, mixed lesion.
9	23	M.	3	15.9	50	5,750	84	3,110	2,875	42	1,540	Some features of glomerulonephritis; dye appeared in urine ten minutes after injection.
Mean values.....				14.8	38		96.4	3,450		59.4	2,150	
Probable error.....				0.54	1.86		1.88	46.2		2.4	91.6	

*Uncorrected for weight of edema.

plasma. The usual secondary cardiovascular signs observed in glomerulonephritis are absent. The blood pressure is not elevated, and anemia is slight or absent. There are no retinal changes. Volhard divided nephrosis into two types, according to the prognosis. One type progresses and terminates with the usual signs of chronic glomerulonephritis; the second has a more favorable prognosis, and persistent albuminuria may be the sole residual abnormality. Most cases of nephrosis represent mixed forms: nephrosis with some features of glomerulonephritis, that is, hypertension, anemia, and so forth.

The mean value for hemoglobin was 14.8 gm. per cent, and the mean value for cells by the hematocrit was 38 per cent. The mean value for blood volume was 96.4 c.c. for each kilogram of body weight, and 3,450 c.c. for each square meter of body surface. The mean plasma volume was 59.4 c.c. for each kilogram, and 2,150 c.c. for each square meter. In four of the nine cases there was mild anemia. In the cases without anemia the average blood volume was 91 c.c. and the average plasma volume was 53 c.c. for each kilogram of body weight. These are values approximately for simple normovolemia. In the four cases of mild anemia, the average blood volume was 102 c.c. and the average plasma volume 70 c.c. for each kilogram—oligocythemic hypervolemia.

The changes in the blood volume and plasma volume in nephrosis incident to diuresis are shown in Table 30. In only one of the cases (Case 6) were the changes of significance, a loss of 610 c.c. of blood, two-thirds of which was plasma. In Case 9, there was an increase of 400 c.c. of plasma; this is not shown in the figures for blood volume because of loss of cells. In the other cases, the variations were negligible.

These data are quite different from those obtained in cases of glomerulonephritis; the mean values for the entire group show, as compared with the mean for normal persons, a slight

TABLE 30
DIURESIS IN CASES OF NEPHROSIS

Case.	Loss of weight, kg.	Change in cells by hemato-crit, per cent.	Blood volume.		Plasma volume.		Duration of diuresis, days.
			Increase, c.c.	Decrease, c.c.	Increase, c.c.	Decrease, c.c.	
1	10	-1					22
3	15	-2			130		24
6	9	+1		610		360	13
7	4	-3		315			30
8	15	-7		220	175		16
9	8	-7			400		11

increase in the whole blood volume, and a definite increase in the plasma volume, according to the corrected body weight. With the decreased cell volume taken into consideration, the status is oligocythemic hypervolemia. In the cases without anemia, the values for plasma volume and blood volume are usually close to that of the mean for normal persons. The status is virtually simple normovolemia. In the cases with mild grades of anemia, the average values indicate oligocythemic hypervolemia. The mean plasma volume for each kilogram in this group with anemia averages 17.5 c.c. greater than the mean value found in the cases of glomerulonephritis.

Darrow collected the volume data in three cases of nephrosis using the dye method according to the uncorrected body weight. Low values were obtained for the blood volume and plasma volume. In one of his cases, following diuresis and after an interval of eight months, the blood volume increased 400 c.c., comprising an increase of both cells and plasma. In another case of his series there was a loss in weight of 5.3 kg. of fluid, with an increase of 600 c.c. of blood volume, mostly plasma.

If his values had been corrected for the weight of the edema fluid, higher values would have been found for the relative blood volume and plasma volume.

Several possible explanations of this high volume of plasma in nephrosis present themselves. It may represent a true dilution phenomenon and an increased amount of water retained in the blood as the result of the edema; the increase of mean plasma volume, about 20 per cent over the normal, without definite increase in the cell volume, would be sufficient to produce mild relative or dilution anemia. However, the absence of changes in the plasma volume, as the result of the disappearance of the edema, is evidence against this assumption. The second possible explanation is that the slight degree of anemia in some of these cases is accompanied by an excessive replacement of plasma, a condition which obtains in some cases of splenic anemia. The third possible explanation concerns itself with the observation of Bennhold, on the rapid disappearance of Congo-red from the circulation in cases of uncomplicated nephrosis and amyloid disease. This phenomenon has been confirmed by Bookman and Rosenthal and by us. A loss of the dye as great as 47 to 55 per cent may occur in one hour. The crucial question in deciding this would rest on the rate of disappearance of the dye within the six-minute period. Therefore, we determined the rate of disappearance of the dye for the three-minute, four-minute, and six-minute periods in four cases of nephrosis. It was shown that the rate of disappearance averaged 1.5 per cent greater than the rate in normal subjects, a difference too small to explain the larger percentage increases in the plasma volume. A further argument against accepting an increased rate of excretion of dye to explain the increased plasma volume, is that the increased values for plasma volume were found only in the cases in which anemia was present. Increased hydrophilic properties of blood and tissues, renal blockage, and de-

creased blood proteins may also be considered. We do not believe, however, that enough data are at hand to decide this question.

In cases of nephrosis with edema but without anemia mean values for blood volume and plasma volume according to corrected body weight correspond with those for normal persons, approximately simple normovolemia. In the cases in which there was mild anemia, the mean blood volume and plasma volume were increased, although they still were within the normal range. The explanation of this increase is not clear.*

The volume changes occurring in a case of nephrosis which gradually passed into glomerulonephritis were those of a gradually decreasing volume of blood and cells without adequate replacement of plasma.

CARDIAC EDEMA (TABLES 31 AND 32)

Eleven cases of valvular and hypertensive cardiovascular disease with cardiac insufficiency and chronic passive congestion were studied. The degree of edema was graded from 1 to 4. Ascites and portal cirrhosis were present in several instances. The usual treatment was used. The blood volume and plasma volume were calculated on the basis of weight of the body in the edema-free period.

When calculated on the basis of body surface and the edema-free weight, a definitely high relative value was obtained in Cases 1, 4, 5, 6, 9, and 11. The plasma volume according to the corrected body weight was found to be abnormally high in Cases 1, 4, 5, 6, 9, and 11. On the basis of body surface, there was an extremely high plasma volume in Cases 5 and 9. In Case 7, in which obesity was marked, a relatively low blood volume according to body weight was present. The mean value for blood volume for the group was 93.9 c.c. for each

* A more complete discussion is given in a recent article.²⁶

TABLE 31
CARDIAC EDEMA

Case.	Age.	Sex.	Grade of edema.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Comment.
						Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	
1	26	F.	3	14.6	89	6,280	112	4,050	8,830	68	2,470	Mitral endocarditis.
2	53	M.	3	16.4	46	4,860	85	3,080	2,650	46	1,675	Hypertension; chronic passive congestion.
3	60	F.	3	14.4	84	5,140	71	2,940	3,390	47	1,985	Myocardial insufficiency.
4	48	M.	2	14.1	40	6,050	108	3,735	3,640	65	2,260	Hypertension; cardiac break.
5	36	M.	4	16.8	96	9,880	96	4,600	5,990	62	2,930	Marked obesity; hypertension.
6	40	M.	3	18.2	97	6,740	107	3,875	4,250	57	2,430	Myocardial disease.
7	44	M.	3	15.9	46	6,170	68	3,100	3,330	37	1,670	Myocardial disease; obesity graded 3.
8	62	M.	3	13.2	83	6,780	78		4,550	52		Aortic endocarditis.
9	38	F.	2	12.7	85	6,440	117	4,180	4,190	76	2,720	Mitral endocarditis; portal cirrhosis.
10	39	F.	1	16.6	46	5,000	88	3,120	2,700	47	1,690	Chronic endocarditis.
11	53	M.	3	15.0	88	6,990	97	3,670	4,340	60	2,280	Hypertension.
Mean values.....				15.3	89.7		93.9	3,640		58	2,180	
Probable error				0.323	1.0		3.4	117.5		2.34	90.04	

kilogram of body weight, and 3,640 c.c. for each square meter of body surface. The mean value for plasma volume was 58 c.c. for each kilogram and 2,180 c.c. for each square meter. The highest blood volume according to body weight was in Case 9. The mean value for the hemoglobin was 15.3 gm. per cent and for cells by the hematocrit 39.7 per cent. In only two cases was there definite anemia (Cases 8 and 9).

Diuresis did not produce a uniform change in the blood volume or plasma volume although in six of eight cases the blood volume increased (Table 32). In Cases 2 and 3, the

TABLE 32
DIURESIS IN CASES OF CARDIAC EDEMA

Case.	Loss of weight, kg.	Change in cells by hematocrit, per cent.	Blood volume.		Plasma volume.		Duration of diuresis, days.
			Increase, c.c.	Decrease, c.c.	Increase, c.c.	Decrease, c.c.	
1	12	+3	160			100	30
2	12	-3	450		375		9
3	4	+5	950		320		10
4	12		260		150		11
5	27	+1		1,550		1,060	19
6	13	-1	120			140	13
7	12	-9		720			12
11	18	+3	210			90	16

blood volume increased significantly in both cells* and plasma. In Case 7 there was a loss of 720 c.c. in cell volume, and in Case 5 there was a decrease of 1,550 c.c. of blood, two-thirds

* It is possible, as in Case 2, to have an absolute increase in cell volume, but a relative decrease as shown by the hematocrit value. That is, the increase in cells was small compared with the increase in plasma.

of which was plasma. In four of the eight cases, significant changes did not occur in the blood volume and plasma volume during diuresis in spite of huge losses of fluid.

The demonstration of increased volume of blood during the stage of edema in cardiac disease is in accord with the observations in experimental chronic passive congestion. Bolton partially obstructed the vena cava in cats; the result was hydremic plethora (oligocythemic hypervolemia), which later became true plethora (polycythemic hypervolemia) by influx of erythrocytes into the blood. He used the Welcker^{109,110} or bleeding method for determining the blood volume. Data were not obtainable during the period of the development of edema in our cases; therefore the changes in the blood volume during this period could not be followed.

The hypotheses advanced to explain the increase in the blood volume in cardiac edema are either that it is a pathologic process in itself or that it is compensatory. If, as Bolton observed, there is in the developing stage of edema an increase of fluid in the blood (oligocythemic hypervolemia, or hydremic plethora), producing dilution, this would indicate a pathologic process. The tissue spaces and serous cavities are filled and further retention of water necessarily occurs in the blood. If cells are thrown into the circulation to maintain the normal relationship of cells to plasma, this phase would probably be a compensatory measure, since cells would be available if the hematopoietic system remained intact. With the onset of diuresis a readjustment is necessary. Fluid passes out and excess cells are present in the circulation. The development of mild jaundice during diuresis, such as was observed in Case 7, associated with a sharp decrease of cells (Table 32) in the blood, suggests that hemolysis occurs for the purpose of ridding the body of excess erythrocytes. This probably is the explanation of icterus neonatorum. Another explanation of the

increase in the quantity of blood is that under special circumstances it may be due to an anoxemic reaction.

The mean value for the blood volume was found to be increased in eleven cases of cardiac edema, according to the corrected body weight. Both plasma and cells are proportionately increased, and the normal ratio of cells to plasma is substantially maintained (simple hypervolemia). The cases in which the relative volume of blood for each kilogram was decreased were explained by the existence of obesity.

During the period of fluid loss, there was an increase in the blood volume in more than half of the cases. In only two were the changes of sufficient magnitude to be considered significant. In two there was a sharp decrease in volume, one due to loss of cells and one to loss of cells and plasma. The increase in the circulating volume of blood is in accord with experimental data.

EDEMA OF DIABETES (TABLE 33)

In the three cases of diabetes mellitus distinguished by edema during the course of treatment in which large quantities of alkalis were given, marked grades of edema were noted. The treatment of the edema consisted in administration by mouth of calcium chloride in massive doses. The loss of weight due to loss of fluid varied from 5 to 13 kg. The volume of blood and plasma was determined during a period of maximal edema and after the completion of diuresis and was calculated for the edema-free body weight. During the period of edema, the blood volume, when calculated on the basis of weight and body surface, was slightly low in Cases 1 and 2, and high in Case 3. In Case 1 plasma volume during the period of edema nearly corresponded with the mean for normal (Table 47) and was increased in Cases 2 and 3 when calculated on the basis of body weight and body surface. Anemia was not present according to the percentage values of hemoglobin; the hematocrit

TABLE 33

EDEMA OF DIABETES FOLLOWING DIURESIS

	Case.	Age.	Sex.	Weight, kg.	Loss of weight, kg.	Grade of edema.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.		
									Total volume, c.c.	C.c. for each kg. body weight.	C.c. for each sq. m. body surface.	Total volume, c.c.	C.c. for each kg. body weight.	C.c. for each sq. m. body surface.
In stage of edema.	1	43	M.	83		2	18.2	40	6,000	85	3,270	3,600	51	1,960
After diuresis. . . .				70	13		12.5	30	6,410	91	3,510	4,490	64	2,450
In stage of edema.	2	30	M.	75		2+	14.5	32	5,820	83	3,180	3,950	57	2,160
After diuresis. . . .				70	5		14.9	33	5,960	85	3,250	4,000	57	2,180
In stage of edema.	3	41	M.	71		3	16.6	37	6,800	108	3,770	4,280	68	2,370
After diuresis. . . .				63	8		14.4	36	5,740	91	3,190	3,670	58	2,040
Average values in stage of edema.								36.3	6,207	92	3,407	3,943	59	2,163

values were definitely decreased in Case 2. The changes in the blood volume and plasma volume following diuresis were not uniform. In Case 1 there was an increase in the total blood volume of approximately 400 c.c. (about 6 per cent), whereas the plasma volume increased 890 c.c. (25 per cent). In this case there was a drop of 25 in the percentage of cells by the hematocrit; there was a somewhat greater percentage decrease in the hemoglobin, and a decrease in the actual circulating hemoglobin of approximately 300 gm. (30 per cent). With this development of actual anemia there was also some degree of anemia due to the dilution which accompanied the increase in the total blood volume and plasma volume. The course of events in Case 2 was not comparable with that in Case 1. In Case 2 there was no significant change in the total blood volume and plasma volume and in the volume relative to body weight and body surface. The degree of diuresis, however, was much less in this case, and brought about a decrease in body weight of

5 kg. In Case 3, there was a decrease in the total blood volume of approximately 1 liter (14 per cent). The actual plasma volume also was decreased approximately 600 c.c. (about 14 per cent). With these sharp changes in the total blood volume and plasma volume, and in the volume relative to body weight and body surface in this case, there was no significant change in the cells by the hematocrit and only a very moderate decrease in the hemoglobin in grams per cent. The loss of weight due to diuresis in this case was 8 kg.

SUMMARY

The fact that varying volume states obtain relative to the blood and plasma values in the different types of edema brings up many problems for consideration. Is the blood playing an active or a passive part in the pathogenesis of edema? If the blood is not an active factor, are the body cells and tissues playing the important part? What part is played by the kidney? Is oliguria due to decreased renal permeability, to lack of availability of water in the blood, or to tissue thirst whereby water is bound and not permitted to reach the kidney or even the blood stream?

In glomerulonephritis we have found that the volume of blood is decreased, due to a decrease in the cell volume. What bearing has this on the urinary output? The fluid part of the blood is not decreased in amount, but the total volume of blood is decreased. Therefore, it might be said, the fluid which is present is not available for excretion and the result is oliguria. The anemia is a characteristic manifestation, but with the loss of erythrocytes the total volume of blood also decreases. Replacement by plasma, such as occurs in ordinary anemia, fails; or if it does occur to some extent, at least it is inadequate for the maintenance of normal blood volume. This suggests the existence of tissue thirst or a hydrophilic condition of the tissues

which in turn may be related to the cause of edema. The increase in blood pressure so usually encountered may have the purpose of aiding in the secretion of urine and may be an attempt to compensate for the low blood volume.

In nephrosis, definite grades of anemia are lacking. Assuming for the present that the blood and plasma values are correct, we find that we have to deal with a slightly increased blood volume and a somewhat greater increase in plasma. Water exists in the blood in abundance so that we appear to be dealing with a dilution phenomenon; yet oliguria and edema are both present. Renal impermeability naturally suggests itself as one factor in the edema. A hydrophilic condition of the blood itself, whereby it holds an excess of water, also seems possible. Edema is extreme in most cases of nephrosis, and it is possible that both the blood and tissues are highly hydrophilic, that the kidney is impermeable, or that all these factors are playing a rôle. The capacity of the tissues to hold water as the cause of the edema has received the greatest support of late. But this will not suffice to explain our observations unless increased hydrophilic properties are also ascribed to the blood. This leads logically to the questions of the binding of water by blood colloids and of the osmotic pressure of blood plasma in nephrosis. The blood proteins are decreased, and the osmotic pressure is disconcertingly low as compared with the normal. Keith and Power, who studied the osmotic pressure of plasma in nephrosis by Govært's method, found that marked diuresis may be induced at times without any discernible change in osmotic values of plasma. Similarly we do not see, when diuresis is induced in nephrosis, uniform directional change in blood volume or plasma volume. Furthermore, to ascribe the changes in osmotic pressure to lipoids fails to clarify the situation materially. We have observed one case (Table 28) in which edema continued throughout the disorder while the

characteristics of the disease passed from those of nephrosis in the early stages of the illness to those of glomerulonephritis in the later stages. The volume states also changed accordingly.

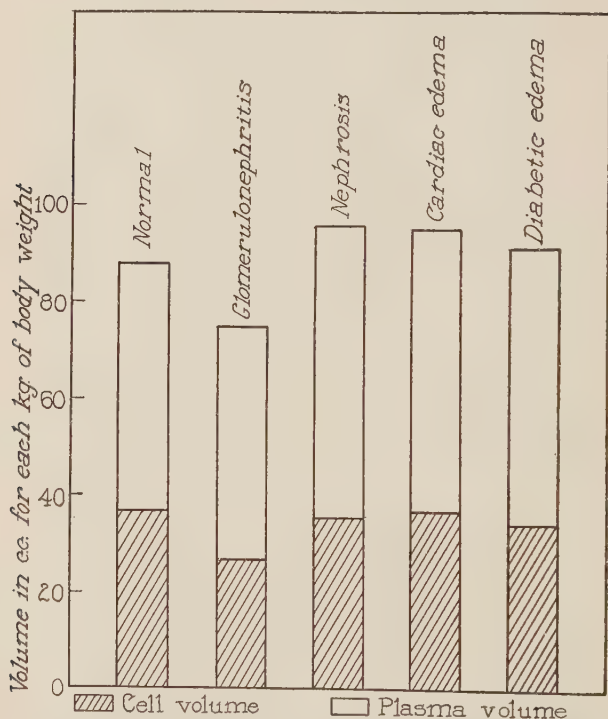


FIG. 16.—Graphic representation of mean values for volume of blood, plasma, and cells in normal conditions and in various states attended by edema.

In cardiac edema, high values for both blood and plasma were the rule. Anemia was lacking. The results conform to Bolton's experimental data in passive congestion: a preliminary rise in plasma and a subsequent corresponding increase in erythrocytes. Simple hypervolemia results. This suggests a

renal block as the cause of edema, rather than any primary disturbance in tissue or blood.

There may be considerable degrees of edema in the presence of (1) low total blood volume and plasma volume within the range for normal persons (glomerulonephritis); (2) increased blood volume and high plasma volume with apparent dilution (page 145) (nephrosis), and (3) increased blood volume and plasma volume without dilution (congestion of cardiac origin). Moreover, diuresis may be induced in all of these conditions without any uniform change either in blood volume or plasma volume. Obviously, the blood can be only one of several factors concerned. Its rôle would seem to be passive rather than active. It is more likely that the changes in blood volume simply reflect changed relationships relative to water between the tissues and kidneys.

The mean values for blood volume and plasma volume in various states of edema are shown in Figure 16.

Chapter XI

DISEASES OF THE VASCULAR SYSTEM

ESSENTIAL HYPERTENSION (TABLE 34)

Ten cases of uncomplicated hypertension of a primary or essential type were studied. Cases in which there was renal or cardiac decompensation and obvious anemia were excluded. The blood pressure readings were high and varying degrees of arterial sclerosis were found in the retinal and peripheral arteries. Cases 4 and 10 represented examples of malignant hypertension with excessively high diastolic pressure and characteristic changes in the fundi.

The mean volume of blood for each kilogram of body weight was 82.5 c.c. and the range was from 59 to 96 c.c. For each square meter of body surface the blood volume was 3,211 c.c. In three cases the patients were obese; in these, the values for blood volume and plasma volume were low and their inclusion in the group produced a mean value slightly less than the mean for normal persons. The mean plasma volume was 50 c.c. for each kilogram of body weight, and 1916.7 c.c. for each square meter of body surface. The mean percentage of cells by the hematocrit was 41.6. The mean value for hemoglobin was 13.7 gm. per cent. According to the relative values for the hemoglobin and for percentage of cells by hematocrit, mild anemia could be considered to be present in five cases; in these, the plasma volume was slightly increased.

The normal values for the blood volume and plasma volume in essential hypertension confirm the data of Keith, Rown-

TABLE 34
ESSENTIAL HYPERTENSION

Case.	Age.	Sex.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood pressure.		Blood.			Plasma.			Comment.
						Systolic.	Diastolic.	Total volume, c.c.	C.c. for each kg. body weight.	C.c. for each sq. m. body surface.	Total volume, c.c.	C.c. for each kg. body weight.	C.c. for each sq. m. body surface.	
1	55	M.	83	19.7	47	210	115	6,490	78	3,310	3,440	41	1,755	Moderate obesity.
2	58	M.	72	14.9	42	200	100	4,960	69	2,680	2,880	40	1,560	General arteriosclerosis.
3	54	M.	116	17.7	41	270	160	6,850	59	2,900	4,040	35	1,710	Severe hypertension; obesity.
4	40	M.	57	13.5	37	240	160	5,340	94	3,275	3,360	59	2,060	Severe malignant hypertension.
5	65	M.	86	16.8	46	190	120	6,410	74	2,890	3,460	40	1,560	Marked general arteriosclerosis with hypertension; obesity graded 2.
6	45	M.	79	10.6	36	210	130	6,490	82	3,380	4,150	52	2,160	Severe essential hypertension.
7	42	M.	70	9.8	39	210	120	6,270	90	3,710	3,830	55	2,265	Moderately severe hypertension.
8	39	M.	73	11.7	39	220	140	6,700	92	3,640	4,090	56	2,220	Severe hypertension.
9	46	M.	76	19.7	46	210	130	7,310	96	3,830	3,950	52	2,070	Severe essential hypertension; arteriosclerosis graded 3.
10	33	F.	54	11.7	38	270	170	4,870	90	3,100	3,020	56	1,920	Malignant hypertension.
Mean values . .			77	13.7	41.6				82.5	3,211		50	1916.7	
Probable error.			3.4	0.66	0.83				2.7	73.8		1.6	59	

tree, and Geraghty. The conception that hypertension may be related to or caused by a large volume of blood in a normal or contracted vascular field is without support. Holman, in a recent article on variations in blood volume in experimental arteriovenous fistula, commented on the nature of the control of blood volume in the body. He raised the question as to whether essential hypertension may not be due to impairment of the mechanism for the control of blood volume. Certainly the data obtained by the dye method show that there is no significant increase in the blood volume or plasma volume or any disturbance in the relationship of cells to plasma. They are comparable to values found in normal subjects of like build. Holman also advanced the hypothesis that cardiac hypertrophy and dilatation are caused by an increase in the blood volume rather than by increased peripheral resistance. The absence of cardiac hypertrophy in many cases of polycythemia vera seems to negate this surmise. Furthermore, in most cases of polycythemia vera in which there is not only marked increase in the circulating volume of blood, but also high values for the viscosity of the whole blood, hypertension is not found. It is observed from Table 34 that Case 1 has high values for the percentage hemoglobin and cells by the hematocrit. This would suggest the possibility of these representing examples of so-called Geisböck's disease. Comparable values are occasionally seen in normal subjects without hypertension. We have encountered two cases of hypertension associated with high erythrocyte counts and percentage of cells. These have been discussed in some detail in Chapter VIII. Our findings concerning volume in hypertension would seem to dispose definitely of Holman's hypothesis.

RAYNAUD'S DISEASE (TABLE 35)

The five patients included in this group represented typical examples of vasomotor neurosis (Raynaud type). The dis-

turbance was bilateral and the usual color changes in response to cold were constant and typical. The trophic disturbances were not those of frank gangrene, but usually consisted of small excavations in the tips of the digits. The functional basis of the disease was evidenced by the presence of pulsating arteries, and by partial, complete, or excessive recovery from the cyanosis on exposure to warmth. The volumes were determined during the period of hospitalization under controlled conditions of environmental temperature.

TABLE 35
RAYNAUD'S DISEASE

Case.	Age.	Sex.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.		
					Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body sur- face.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body sur- face.
1	28	M.	15.6	40	5,130	90	3,010	3,080	54	1,810
2	26	F.	14.7	34	4,000	89	2,120	2,640	59	1,860
3	23	F.	13.0	37	3,500	81	2,500	2,210	51	1,580
4	30	F.	12.6	42	4,970	101	3,360	2,880	59	1,940
5*	33	M.	17.7	41	6,230	105	3,660	3,680	62	2,160
Average			14.72	38.8	4,766	93.2	2,930	2,898	57	1,870

* Subsequent developments have shown that this case was probably an example of thrombo-angiitis obliterans.

The average volume of blood was 93.2 c.c. for each kilogram of body weight or 2,930 c.c. for each square meter of body surface. In Case 5 there was a blood volume for each kilogram of body weight of 105 c.c. with a slightly high plasma volume for each kilogram, 62 c.c. (simple hypervolemia). The average volume of plasma was 57 c.c. for each kilogram of body weight,

and 1,870 c.c. for each square meter of body surface. Anemia of a mild degree was present in Cases 3 and 4, with blood volume and plasma volume for each kilogram in the latter; this is high but within the range of normal. The increased volume of blood for weight in these cases could be due to the low body weight, the average of which was 50 kg., with an average height of 165 cm. According to body surface, the blood volume was decreased as compared with the mean of that in the underweight groups of normal men and of normal women (Table 8).

Environmental changes.—Studies of the blood volume and plasma volume were made in high and in low environmental temperatures (Table 36) in three cases of Raynaud's disease. The variations observed were not more constant than those in the normal subject under similar variations in environmental temperature. A constant or directional shift was not noted, ex-

TABLE 36
ENVIRONMENTAL CHANGES IN RAYNAUD'S DISEASE

Case.	Age.	Sex.	Date.	Room temperature, ° C.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Condition of patient.
1	28	M.	1/18/24	25	15.6	40	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
			1/23/24	17	18.8	44	4,800	84	2,820	2,690	47	1,580	Warm.
Change, per cent.						+10	-6	-7	-6	-13	-13	-13	Chilled at 17° C.
2	26	F.	6/ 3/24	38	14.7	34	4,000	89	2,120	2,640	59	1,860	Sweating; skin warm.
			6/ 4/24	19	12.7	36	4,000	89	2,810	2,560	57	1,800	Cyanotic; shivering.
Change, per cent.						+6			+32.5	-3	-3	-3	
3	30	F.	1/26/24	30	9.8	35	4,190	85	2,820	2,720	56	1,840	Flushed; sweating.
			1/27/24		12.6	42	4,970	101	3,360	2,880	59	1,940	Cyanotic; chilled.
Change, per cent.						+20	+19	+19	+19	+6	+5	+5	

cept in the percentage of cells by hematocrit, which increased with lowered environmental temperature. In Case 3 there was an increase in the blood volume of 19 per cent, which probably was of significance. This was represented largely by the increase in the cell volume. In Cases 1 and 2 there was a definite increase in the percentage of cells, but the decrease in the volume of plasma balanced the increase in the cells; thus significant changes were not observed in the total volume of blood.

THROMBO-ANGIITIS OBLITERANS (TABLE 37)

Six cases of this disease were studied. There was thrombosis of the main arteries of the legs of these patients to and above the popliteal arteries; gangrene of some degree was present in the extremities of each. In one case (Case 3) the patient was aged sixty-one years. The diagnosis of thrombo-angiitis obliterans was justified on the basis of long history, dating over a period in excess of ten years; it was not proved pathologically. The diagnosis in the other cases was proved pathologically

TABLE 37
THROMBO-ANGIITIS OBLITERANS

Case.	Age.	Sex.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Comment.
					Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	27	M.	14.1	49	6,590	108	3,910	3,360	55	2,000	Gangrene of foot.
2	25	M.	14.5	47	6,090	103	3,570	3,230	55	1,890	Trophic ulcer of feet.
3	61	M.	18.1	44	5,790	95		3,240	53		Gangrene of toes, long history.
4			16.7	47	6,120	101	2,470	3,280	54	1,915	
5	29	M.	14.2	45	7,200	106	3,890	3,960	58	2,140	Early manifestation.
6	32	M.		49	6,720	108	4,280	3,430	60	2,180	Early gangrene.
Average.....			15.5	47	6,420	103	3,624	3,416	55.8	2,250	

either by excision of a thrombosed vein or by pathologic studies on the amputated leg.

The average values for the group were as follows: body weight, 61 kg.; height, 170 cm.; blood volume, 103 c.c. for each kilogram of body weight and 3,624 c.c. for each square meter of body surface. The average percentage of cells by the hematocrit was 47, a slightly high value according to our normal standards. The average plasma volume was 55.8 c.c. for each kilogram of body weight. Anemia was not definite in any case.

The blood volume and plasma volume were definitely increased in this small group of cases; the volume status was simple hypervolemia. The cells and plasma were increased proportionately. This increased volume of blood for the group is not entirely explained by the slight degrees of underweight of the patients. If the volume of the blood is calculated according to ideal weight for height and age, an increased value would still be obtained, 94 c.c. for each kilogram. The increase in blood is present not only on the basis of body weight, but also on that of surface area.

Increased viscosity of the blood has been advanced as one of the factors in the production of thrombosis in this disease. The studies we have carried out have shown fairly normal values for viscosity of the blood. The response in the volume of blood to the shutting off of certain portions of the vascular tree has not, to our knowledge, been studied. It is necessary that further work be done on this group of cases before any statement can be made as to the basis of the increase in the volume of blood.

ARTERIOSCLEROTIC DISEASE IN THE LEGS WITH OCCLUSION OF THE ARTERIES AND GANGRENE (TABLE 38)

Three cases of this type were studied. The ages of the patients were fifty-two, sixty-eight, and fifty-one years. In Case

1, according to body weight and body surface, the blood volume and plasma volume were increased. The patient's weight was 62 kg. and the height was 176 cm. According to the ideal weight and height for age, the patient was definitely underweight. If the blood volume was calculated according to ideal weight, strictly normal values would be obtained. Likewise, in Case 3, the patient was definitely underweight for his age and height, and when calculated according to his ideal weight,

TABLE 38
ARTERIOSCLEROTIC DISEASE WITH OCCLUSION

Case.	Age.	Sex.	Hemoglobin, gm. in each 100 c.c.	Cells by hematocrit, per cent.	Blood.			Plasma.		
					Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	52	M.	15.7	40	6,660	107	3,820	4,000	64	2,300
2	68	M.	14.8	38	5,470	87	3,110	3,390	54	1,925
3	51	M.	20.2	43	7,020	106	3,750	4,000	61	2,140
Average.			16.9	40.3	6,383	100	3,560	3,796.6	59.6	2,121.6

strictly normal values would be obtained for the blood volume and plasma volume in relation both to weight and area. The average values in this small group indicated that the volume status was simple hypervolemia. The percentage of cells by the hematocrit was strictly normal. In one case (Case 3) the percentage of hemoglobin for each 100 c.c. of blood was high.

ARTERIOVENOUS FISTULA (TABLE 39)

Seven cases of arteriovenous fistula were studied. Three were of the congenital type and four were of the acquired type. In the congenital type the vessels of the hands, feet, and arms

were involved. There were marked trophic changes in the distal areas. The veins proximal to the fistula were dilated and showed the effects of arterialization of structure and of content. In this form of fistula the communications are multiple. The cases of the acquired types of arteriovenous communication involved respectively the axillary vein and artery, femoral vein and artery, carotid artery and jugular vein, and one involved the intracerebral vessels, probably the carotid artery and cavernous sinus. The duration of the acquired types varied from three months to twenty-six years.

The average value for the blood volume was 94.3 c.c. for each kilogram of body weight, and 3,404 c.c. for each square meter of body surface. The range was from 73 to 124 c.c. for weight and 2,755 to 4,440 c.c. for area. In only one case was a strikingly high volume of blood noted, 124 c.c. for each kilogram; there was a disproportionate increase in plasma.

The average value for the plasma volume was 57.2 c.c. for each kilogram and 2,075 c.c. for each square meter. The range was from 41 to 81 c.c. according to weight, and from 1,570 to 2,890 according to area.

The average value for hemoglobin was 15.2 gm. for each 100 c.c. of blood and for the percentage of cells by the hematocrit, 39.5. The average value for erythrocytes was 4,450,000 for each cubic millimeter. In one case there was mild anemia. None of the subjects in this group was obese or abnormally thin.

The circulation suffers marked disturbance in the presence of an abnormal communication between the artery and vein. Holman has shown that the size and duration of the fistula are proportionate to the circulatory defect. The systemic effects depend on the shunting of variable amounts of arterial blood directly into the venous circulation. This constitutes a loss to the circulating arterial blood, and compensatory measures to

TABLE 39
ARTERIOVENOUS FISTULA

Case.	Age.	Sex.	Hemoglobin, gm. in each 100 c.c. of blood.	Erythrocytes, in each cu. mm., millions.	Cells by hematocrit, per cent.	Blood.			Plasma.			Comment.
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	80	M.	15.0	4.68	48	5,180	73	2,755	2,925	41	1,570	Congenital, involving right arm.
2	20	M.	15.9	4.15	42	5,460	90	3,035	3,170	52	1,760	Congenital, vessels of right arm.
3	19	M.	15.3	4.97	35	7,470	124	4,440	4,855	81	2,890	Traumatic, left femoral.
4	46	M.	15.6	4.50	37	6,070	101	3,610	3,830	64	2,280	Traumatic, right carotid artery and jugular vein.
5	21	M.	17.1	4.53	40	6,500	86	3,510	3,920	52	2,120	Traumatic between the axillary artery and vein.
6	48	M.	14.3	4.38	42	5,050	93	3,235	2,950	55	1,890	Pulsating exophthalmos; probably lesion of the cavernous sinus and internal carotid artery.
7	16	F.	19.3	4.57	38	5,225	93	3,245	3,240	58	2,015	Congenital, involving vessels of lower part of right leg.
Average.....			15.2	4.45	39.5	5,843.5	94.3	3,404	3,555.7	57.2	2,075	

maintain the systemic blood pressure are necessary. Holman suggested that an increase in the circulating volume of blood occurs as one measure to increase or maintain the systemic blood pressure. His experimental studies, in which he utilized the dye method for determining the blood volume, show that the production of a fistula increases the volume of blood and that the amount of blood diminishes again when the fistula is closed.

The clinical studies seem to bear out this conception and for the group the average values for volume of blood are approximately 7 c.c. greater for each kilogram of body weight than the mean for normal persons. The increase is due largely to an increase in plasma, but the normal ratios are fairly well maintained. The effects of operation have been studied. In four cases in which the vessels were ligated or an extremity was amputated, a decrease occurred in the absolute volume of blood and in the volume relative to body weight and body surface. In two cases of these four, the plasma volume decreased and in two it was not changed. The possibility that these changes were due to blood lost at operation could not be excluded.

Chapter XII

DISEASES OF THE ENDOCRINE GLANDS

MYXEDEMA (TABLE 40)

In ten cases of myxedema determinations were made of the blood volume and plasma volume. The average loss of weight in five cases incident to thyroid medication was 8 kg. Corrections for body weight were made in the post-edema period. If this was not possible a correction was made on the basis of previous normal weight. The basis for the correction of weight in this group is not as accurate as in the cases of renal and cardiac edema because the weight loss incident to treatment of myxedema is not entirely that of fluid but includes loss of body protein. Table 40 shows the relative volume of blood and plasma according to the uncorrected and corrected body weight. The differences were not marked; the mean data are presented on the basis of both the corrected and the uncorrected body weight. Anemia in some degree was present in seven cases. In Cases 3, 4, and 5 the grades of obesity were moderate.

The blood volume according to both corrected and uncorrected body weight was below the mean for normal persons in all but one case (Case 6). The mean value for the group was 66 c.c. for each kilogram of corrected body weight or 2,680 c.c. for each square meter of uncorrected body surface. The mean volume of plasma was 48 c.c. for each kilogram of corrected body weight or 1,780 c.c. for each square meter of uncorrected body surface. The mean value for hemoglobin was 13.3 gm. per cent and for the cells by the hematocrit 34.6 per cent. In

TABLE 40

MYXEDEMA

Case.	Age.	Sex.	Weight, kg.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.				Plasma.				Basal metabolic rate.
						Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each kg. of corrected body weight.	C.c. for each sq. m. of body surface.	
1	62	F.	67	13.0	28	4,060	61	69	2,270	2,920	44	49	1,640	-22
2	37	M.	73	14.7	33	4,630	63	66	2,475	3,100	42	44	1,660	-27
3	50	F.	88	8.5	27	5,040	57	64	2,570	3,670	42	46	1,860	-28
4	45	M.	85		40	5,550	65	69	2,690	3,330	39	41	1,620	-34
5	56	F.	85	11.9	33	4,750	56	57	2,510	3,180	37	40	1,680	-22
6	32	M.	74	14.5	36	7,030	95	105	3,820	4,500	61	67	2,440	
7	40	F.	64		39	4,280	67	67	2,530	2,610	41	40	1,550	-22
8	60	F.	70	13.4	33	4,040	58	63	2,380	2,700	39	42	1,590	-30
9	47	F.	75	13.1	32	5,300	70	75	2,860	3,610	48	51	1,950	-21
10	40	F.	68	16.4	40	4,680	69	75	2,670	2,810	41	51	1,600	-21
Mean values . .			75.5	13.3	34.6		66	70	2,680		43.5	48	1,780	
Probable error,			1.8	0.56	0.97		2.4	2.74	94.4		1.5	1.6	58	

only one case (Case 6) was the plasma volume relative to body weight increased.

The changes during administration of thyroid were not constant or uniform. In Case 1 (Table 41) there was an increase of 880 c.c. of blood, of which 540 c.c. was plasma. In Case 3 there was a moderate loss of plasma with an increase in the volume of cells without significant changes in the total blood volume. In Cases 5 and 18 there was no significant change. In Case 6 there was a decrease of 850 c.c. in volume of blood, a third of which was plasma and the remainder of which was cells.

The blood volume and plasma volume in myxedema during the period of edema were relatively low, both according to body weight and to surface area, with a decreased ratio of cells

TABLE 41
THYROID MEDICATION IN CASES OF MYXEDEMA

Case.	Loss of weight, kg.	Change in cells by hematocrit, per cent.	Blood volume.		Plasma volume.		Cell volume.	
			Increase, c.c.	Decrease, c.c.	Increase, c.c.	Decrease, c.c.	Increase, c.c.	Decrease, c.c.
1	8	+2	880		540		340	
3	9	+8		50		430	380	
5	6					110		
6	7	-5		850		230		610
8	10	-3		80		150		

to plasma (cligocythemic hypovolemia). The mean volume of blood for each kilogram of corrected body weight was about 17 c.c. less than the mean for normal persons. The mean volume of plasma according to corrected body weight was less than normal. Anemia in some degree occurs in most cases. Both the plasma volume and cell volume were decreased. Following thyroid medication and loss of weight (loss of both fluid and body protein) the changes in volume did not correlate with the increase in the metabolic rate and clinical improvement. The anemia did not improve greatly, as shown by the percentage of cells by the hematocrit or by the cell volume. Many of the variations noted were not significant.

Thompson found a relationship between the plasma volume and the basal metabolic rate in myxedema. His data show an average increase of 28.5 per cent in the plasma when calculated on the basis of body surface, following thyroid medication. Increases of 25 per cent in the blood volume frequently were observed. His data gave an average blood volume of 63 c.c. and a plasma volume of 35.4 c.c. for each kilogram of uncorrected body weight (hypovolemia) for the nine cases of myxedema before treatment. The mean values in our series of

ten cases during the period of edema gave comparable values of 66 c.c. of blood and 43 c.c. of plasma for each kilogram of corrected body weight.

We did not observe increases in the plasma volume with thyroid medication comparable to those observed by Thompson. We made only a single determination in the period when the rate of metabolism was low and another single determination when the rate was high. Thompson's data are much more complete and it should be noted that the increases occurred in the actual values for blood volume and plasma volume and not in the values relative to body weight and body surface.

The existence of anemia in the cases of myxedema would explain the low blood volume, but, contrary to the usual observations in anemia, compensatory increases in the plasma do not occur, as shown by the mean values. Similar failure of plasma replacement is observed in some cases of renal edema.

HYPERTHYROIDISM (TABLE 42)

Four cases of hyperthyroidism have been studied. The clinical picture was marked and the basal metabolic rate, high. The average values for the blood volume were fairly high as compared with the mean for normal persons. The range was from 79 to 109 c.c. for each kilogram with an average of 96.2 c.c. for each kilogram and 3,420 c.c. for each square meter. The average plasma volume was 58 c.c. for each kilogram and 2,067.5 c.c. for each square meter. The increased blood volume is due to both cells and plasma, maintaining practically the normal ratios (simple hypervolemia). Anemia was not present in any case. The average value for the percentage of hemoglobin was 14.3 and for the cells by the hematocrit, 39.5. The average body weight was 60.7 kg.

On the basis of body weight the average blood and plasma values were especially high when compared with the mean for

TABLE 42
HYPERTHYROIDISM

Case.	Age.	Sex.	Weight, kg.	Body surface, sq. m.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Loss of weight, kg.	Basal metabolic rate.
							Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.		
1	18	F.	50	1.46	14.5	39	5,040	100	3,450	3,070	61	2,100		+50
2	27	F.	53	1.56	14.3	40	5,120	97	3,280	3,075	58	1,970	11.4	+63
3	49	M.	73	1.92	14.5	40	5,780	79	3,010	3,460	47	1,800		+47
4	34	M.	67	1.85	14.1	39	7,290	109	3,940	4,440	66	2,400	10.0	+53
Arithmetic average...			60.7	1.69	14.3	39.5	5,807.5	96.2	3,420	3,511	58	2,067.5	10.7	+53.2

normal persons. The blood contained about the normal ratio of cells to plasma. This form of hypervolemia is similar to that observed in certain types of circulatory disease, chronic passive congestion, and arteriovenous fistula. The basis of the apparent increase in the blood volume in cases of hyperthyroidism is not clear. Two explanations present themselves. First, that it represents a compensatory or pathologic manifestation of the disease and is due to an enlarged circulatory bed; second, that the increase in blood volume may be only apparent, and due to loss of body weight.

If the blood volume is calculated in the subjects in this group on the basis of their ideal weight for age and height, average values will be found of 85 c.c. of blood for each kilogram of body weight, and 52 c.c. of plasma, values almost exactly in accordance with mean values for normal persons. In two of the cases the loss of weight incident to the disease was 11.4 and 10 kg., respectively.

It would be necessary to collect data on a larger group of cases during the hyperthyroid stage, and after recovery had

taken place, in order to draw conclusions on the volume status. It would seem reasonable to assume that the blood volume would be increased in this disease* because of the vascular dilatation that is present and by contrast to assume the existence of relatively low blood volume in cases of myxedema.

ADDISON'S DISEASE (TABLE 43)

Volume determinations were carried out in twelve cases of this disease. Each case represented a typical example, with pigmentation, low blood pressure, asthenia, and gastro-intestinal disturbances. A previous examination of the data concerning the blood in seventeen cases was made by Brown and Roth,²⁵ and Rowntree investigated the data in a larger group. Eighteen studies of volume were carried out on twelve patients. In Case 4, four consecutive determinations were made over a period of five years, and in Cases 7 and 9, two determinations were carried out at intervals of thirty to sixty days.

For the group, the mean blood volume for each kilogram of body weight was 87.3 c.c., and for each square meter of body surface the mean blood volume was 2,900 c.c. The mean value for the plasma was 54.3 c.c. for each kilogram of body weight, and 1,850 c.c. for each square meter of body surface. The volume status was to all intents and purposes simple normovolemia. The mean value for hemoglobin was 13.3 gm. per cent, and for percentage of cells by hematocrit was 35.8. The mean body weight was 57.5 kg. Several of these patients were definitely underweight. None was obese. The blood volume and plasma volume relative to body weight and body surface varied considerably in the individual cases. In three cases (Cases 2, 4, and 8) there was 100 c.c. or more of blood for each kilogram of body weight. In Cases 3, 5, and 9, values less than 80 c.c. for each kilogram were obtained in one of the several

* In hyperthyroidism the minute volume output of the heart is increased.

Case.	Date.	Age.	Sex.	Weight, kg.	Body surface, sq. m.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Clinical condition.
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	9/14/22	53	M.	52	1.59	8.8	33	4,260	82	2,680	2,860	55	1,800	Improved.
2	9/14/22	26	M.	62	1.79	14.5	43	6,240	100	3,480	3,550	57	1,970	Markedly improved.
3	11/ 2/22	42	M.	50	1.57	14.5	30	3,920	78	2,500	2,740	55	1,750	Improved slightly.
4	5/ 3/23	50	M.	58	1.71	15.7	39	4,820	83	2,820	2,940	51	1,720	Poor.
	8/ 1/23			64	1.79	14.2	38	5,860	92	3,270	3,640	57	2,030	Improved.
	2/26/24			63	1.77	15.5	37	6,120	97	3,450	3,850	61	2,180	Markedly improved.
	5/22/28			60	1.75	15.6	42	6,730	112	3,840	3,920	65	2,240	Markedly improved.
5	8/18/23	56	F.	39	1.32	11.3	27	2,900	75	2,200	2,120	55	1,590	Poor. Died twenty days later.
6	6/ 7/23	31	M.	65	1.79	16.4	41	5,330	82	3,000	3,140	48	1,775	Mild shock. Poor condition.
7	3/24/24	24	M.	59	1.65	14.7	32	4,750	80	2,830	3,240	55	1,950	Mild shock.
	5/ 9/24			59	1.68	14.6	35	4,940	84	2,940	3,210	54	1,910	Slightly improved.
8	9/15/22	30	M.	60	1.75	13.4	30	6,270	104	3,580	3,760	63	2,150	Improved.
	4/ 3/24			60	1.75	15.2	33	4,980	83	2,850	3,330	55	1,900	Good.
9	3/29/28	45	M.	56	1.60	10.5	38	4,150	74	2,590	2,570	46	1,600	Collapse.
	4/16/28			53	1.55	10.7	38	5,230	99	3,370	3,240	61	2,090	Died 6/4/28.
10	5/30/24	46	M.	55	1.65	12.5	32	4,760	87	2,880	3,240	59	1,960	Ambulatory.
11	5/ 3/28	36	F.	64	1.70	12.2	36	5,460	85	3,215	3,490	55	2,050	General condition good.
12	5/ 3/28	48	M.	60	1.64	14.9	43	5,170	86	3,150	2,650	49	1,800	Fairly well compensated.
				57.5	1.90	13.3	35.8	4,792	87.3	2,900	3,067	54.3	1,850	
Mean values*				1.4	0.37	0.42	1.1	184	1.8	73.7	79	0.8	32	
Probable error														

* Determinations made from first reading in each case.

determinations. Anemia according to both the hemoglobin and hematocrit values was present in Cases 1, 5, 8, 10, and 11. In only one case (Case 1) was the degree of anemia marked. In the cases with anemia the plasma volume for each kilogram of body weight was normal or slightly increased. The lowest blood volume relative to body weight usually occurred in the cases with anemia. The mean value for plasma volume for each kilogram of body weight was slightly increased, but was decreased according to body surface. During the period of improvement in Cases 4, 8, and 9 plasma volume according to body weight and body surface was in excess of that found in the normal subjects. Significantly low plasma volumes were not found.

The fluctuations in the blood volume and plasma volume during treatment were of greatest interest. The patient corresponding to Case 4, when first seen in 1923, had 83 c.c. of blood and 51 c.c. of plasma for each kilogram of body weight. At this time he was extremely asthenic, his blood pressure was very low, and he was too weak to indulge in mild degrees of activity. There was no anemia at this time. Three months later, with improvement in his physical condition, blood volume had increased over 1,000 c.c. and the plasma volume 700 c.c. After a second interval of one year blood volume had further increased 260 c.c. and plasma volume about the same amount. Approximately four years later this patient was still under observation, had continued treatment, had resumed work as a farmer, and was in a fairly healthy condition as long as he continued the treatment with epinephrine. The actual blood volume at that time again had increased 610 c.c.; and the plasma, 70 c.c.; he had 112 c.c. of blood and 65 c.c. of plasma for each kilogram of body weight, and the values for the percentage of cells by the hematocrit and for the concentration of hemoglobin were substantially normal. In other words, in this

patient the amount of blood had markedly increased without disturbing the ratio of cells to plasma. Definite changes were not noted in Case 7 over a time interval of two months. There was no significant change in the clinical status of the patient during this interval. In Case 8 both determinations were carried out while the patient was in a fairly good condition. At the time of the first determination there were 104 c.c. of blood and 63 c.c. of plasma for each kilogram of body weight; there was a decrease in the percentage of cells by hematocrit and in the amount of hemoglobin as compared to the mean for normal persons. Two years later the blood volume had decreased to 83 c.c. and the plasma volume to 55 c.c. for each kilogram, with an increase in cells by the hematocrit and in the concentration of hemoglobin. In Case 9, the first determination was carried out March 29, 1928, at which time the patient entered the hospital in collapse and presenting the shock-like condition noted during periods of suprarenal insufficiency. At the first determination there were 74 c.c. of blood and 46 c.c. of plasma for each kilogram of body weight. Following treatment, which consisted of the intensive Muirhead regimen and fluids given subcutaneously and intravenously, the actual blood volume increased approximately 1,000 c.c., of which 670 c.c. was plasma. This was accompanied with distinct but temporary improvement in the patient's condition. The patient died two months later.

Addison described anemia as an integral feature of this disease. Subsequent workers, using quantitative methods for measuring concentration of the erythrocytes and hemoglobin, found that anemia usually was absent. One of us (Rowntree⁹¹) in forty-three cases found normal average values for the number of erythrocytes and percentage of hemoglobin in approximately 75 per cent of cases. In our laboratory²⁵ it was shown that anemia was exceptional in Addison's disease and that

when it was present it was mild. It also was shown that anemia was not produced by dilution of the blood as was averred by Averbeck. This agrees with the observations of Dock in four cases and with Osler's statement that when anemia is present in Addison's disease it is due to an actual decrease in the number of erythrocytes and not to dilution. Calculated on the basis of the mean values, we found that there were 30 c.c. of cells and 11 gm. of hemoglobin for each kilogram of body weight, indicating for the group a mild grade of actual anemia. Dilution was not present since the mean value for the blood volume was approximately the same as that for normal persons. In the cases of Addison's disease, in which anemia was distinct, the replacement factor was 43 per cent. It would seem from our studies that there is a relationship between the blood volume and the clinical status of the patient. The patients in shock and collapse showed the lowest volume of blood according to body weight; improvement was followed by an increase both in blood volume and in plasma volume. In other words, changes in the clinical status were associated with changes in the volume of blood and plasma. With the exception of Case 8, the studies of the blood of patients who lived over a fairly long interval of time and who showed clinical improvement revealed that there had been increases in the actual and relative volume of blood and of plasma.

DIABETES INSIPIDUS (TABLE 44)

Volume determinations were made in four typical cases of diabetes insipidus during the period of excessive ingestion of water, in three before, and in one case during the administration of pituitary extract. The volume of blood for each kilogram of body weight was approximately normal in the first three subjects; the average was 81 c.c. for each kilogram of body weight and 2,923 c.c. for each square meter of body sur-

face. The average plasma volume for each kilogram in these three cases was 54.3 c.c. for weight and 1,940 c.c. according to area. The volume status in the first three cases was that of mild oligocythemic hypovolemia. The values for hemoglobin were normal.

TABLE 44
DIABETES INSIPIDUS

Case.	Age.	Sex.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.			Comment.
					Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	
1	16	M.	15.6	34	4,000	78	2,600	2,640	52	1,710	
2	41	F.	16.7	33	3,920	69	2,500	2,630	46	1,670	
3	19	M.	14.7	34	6,610	96	3,670	4,390	65	2,440	
4	27	M.	16.8	44	6,430	107		3,600	60		With deprivation of water.
				41	6,700	111		3,960	66		Water intoxication phase.
			17.1	45	6,175	103		3,390	56		Mild symptoms of water intoxication during treatment.

In Case 4 three determinations were made during a period of water intoxication and water deprivation. The blood volume and plasma volume were high during water deprivation and increased still further during the phase of water intoxication, and were diminished during the period of treatment.

The water metabolism in diabetes insipidus has been studied by Weir, Larson and Rowntree, and by Snell and Rowntree. The changes observed in experimental and clinical studies on water intoxication have been great enough to disturb the electrolytes of the blood and certain other physical factors. In the experimental animal, the changes observed by Greene and Rowntree, with excessive administration of water, have been of considerable magnitude. Increases of 14 per cent in the

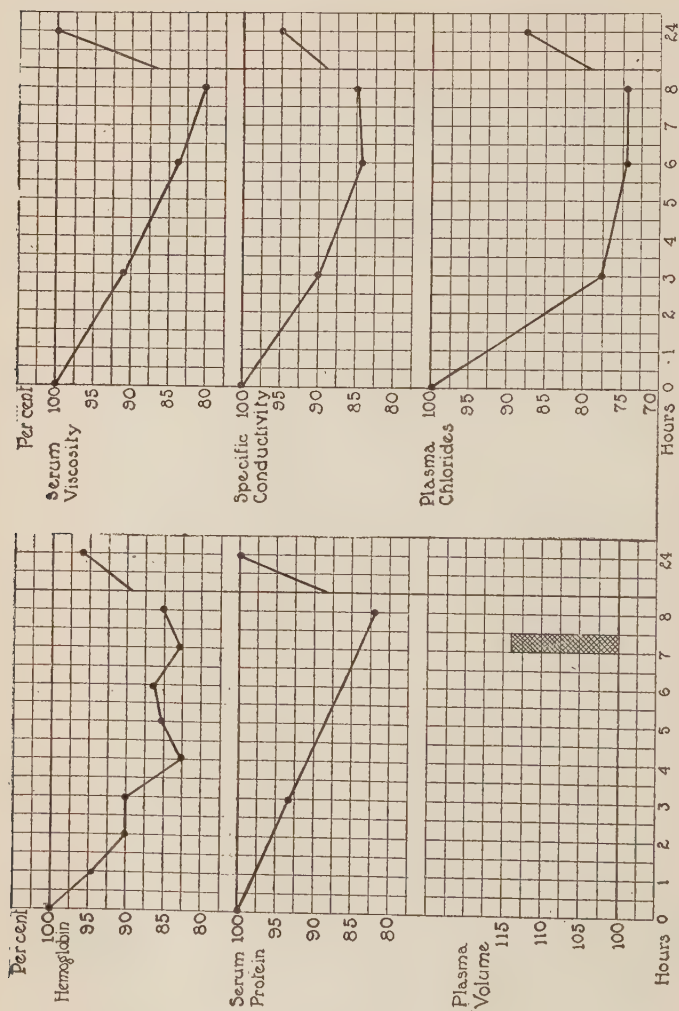


Fig. 17.—Chart showing the average change in various constituents of the blood in percentage of initial value. Values obtained in experimental animals following excessive intake of water. (After Greene and Rowntree.)

plasma volume were demonstrated. Serum protein, hemoglobin, serum viscosity, specific conductivity, and plasma chlorides were comparably reduced (Fig. 17). Apparently,

transitory dilution processes can be produced experimentally. Snell and Rowntree found in a case of diabetes insipidus a distinct increase in the plasma volume during tremors induced by excessive ingestion of water. The actual cell volumes were nearly constant (Case 4, Table 44). The changes in the different blood factors, such as chlorides and serum proteins, give confirmatory evidence of the accuracy of the dye method for estimating the plasma volume. The mechanism of intake and output is sufficiently balanced to prevent water intoxication and changes in the blood volume and plasma volume. If, however, volume changes of any magnitude occur, convulsive seizures may appear with evidence of severe physiochemical disturbance in the blood and in the nervous system. This has been shown both in man and in the experimental animal.

DIABETES MELLITUS (TABLE 45)

In seven cases, single determinations of the volume of blood and plasma were made during the period of hyperglycemia. Anemia was present in one case. The average value for hemoglobin was 13.5 gm. per cent. The average percentage of cells, as measured by the hematocrit, was 35.3. The average value for blood volume was 81 c.c. for each kilogram of body weight, and 3,071.4 c.c. for each square meter of body surface. The range was from 70 to 91 c.c. for each kilogram. The average plasma volume was 52.5 c.c. for each kilogram and 1,978.5 c.c. for each square meter of body surface. The range varied from 45 to 74 c.c. for each kilogram. Volume of plasma higher than the upper limit for normal persons was present in Case 3 and marked anemia existed. In one case which was complicated by diabetic coma, and which is not included in the table, the blood volume was 122 c.c., and the plasma volume, 60 c.c. for each kilogram of body weight. Following treatment, these values increased respectively to 127 c.c. and 72 c.c., during which time

the weight increased 4 kg. The cells by hematocrit decreased from 51 to 43 per cent, and the hemoglobin decreased from 16.3 to 13.4 gm. per cent.

TABLE 45
DIABETES MELLITUS

Case.	Age.	Sex.	Weight, kg.	Body surface, sq. m.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Blood.			Plasma.		
							Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.
1	47	M.	89	2.06	14.5	43	7,040	79	3,420	4,045	45	1,965
2	43	M.	67	1.80	14.2	37	5,440	81	3,020	3,428	51	1,900
3	43	M.	65	1.74	5.8	14	5,580	86	3,200	4,800	74	2,750
4	57	M.	63	1.71	17.1	40	5,435	86	3,175	3,260	52	1,900
5	65	M.	80	1.92	15.6	43	7,260	91	3,780	4,138	52	2,155
6	46	M.	59	1.70	12.2	37	4,395	74	2,585	2,770	47	1,625
7	32	F.	54	1.62	15.0	33	3,760	70	2,320	2,520	47	1,555
Average.....			68.1	1.79	13.5	35.3	5,558.5	81	3,071.4	3,565.8	52.5	1,978.5

Approximately simple hypovolemia exists in uncomplicated diabetes mellitus, according to our data. Since anemia was present in only one case, variations were not noted in the blood volume or plasma volume in the uncomplicated cases. The values in the case with coma were unique. Following treatment with insulin and forced fluids, the plasma volume increased 910 c.c., producing a fall in the values for the cells and hemoglobin. This represents true dilution. Villa observed the effects of insulin on the blood volume and found decreases of 11 per cent after the intramuscular injection of 50 units of insulin. We have not made comparable studies.

Chapter XIII

MISCELLANEOUS DISEASES

EMPHYSEMA, CHRONIC BRONCHITIS, AND ASTHMA (TABLE 46)

Twelve cases in which there were varying grades of emphysema and chronic bronchitis, with cyanosis, were reported by Lemon. Eleven of the patients were men and one was a woman. The possible variations in the volume of the blood resulting from deficient oxygenation of the pulmonary blood were investigated particularly. The appearance of many of these patients suggested the existence of polycythemia. Peripheral and facial cyanosis, the congested appearance of the mucous membranes, and the dilated vessels of the skin of the face associated with variable grades of dyspnea were fairly common.

The mean value of hemoglobin was 16.5 gm. per cent. In six cases values were more than 16.4 gm. per cent, the mean value for normal males (Table 8). The mean percentage of cells of the hematocrit was 42.5 and the range was from 34 to 56 per cent. The erythrocytes varied from 4,050,000 to 6,860,000 with a mean of 5,020,000 for each cubic millimeter. In four cases the values were more than 5,000,000 for each cubic millimeter. In only two cases (Cases 3 and 9) were the percentage of cells and the number of erythrocytes high. The blood volume ranged from 82 to 103 c.c. for each kilogram of body weight with a mean of 92.2 c.c.; there was only one case in which this value was more than 100 c.c. The blood volume was 3,367 c.c. for each square meter of body surface. The mean plasma

TABLE 46
VOLUME OF BLOOD AND PLASMA IN CASES OF CHRONIC BRONCHITIS, EMPHYSEMA, AND ASTHMA

Case.	Age.	Sex.	Weight, kg.	Ideal weight for height and age.	Hemoglobin, gm. in each 100 c.c. of blood.	Cells by hematocrit, per cent.	Erythrocytes, in each cu. mm., millions.	Blood.				Plasma.			Cells.	
								Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each kg. of ideal body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.
1	64	M.	66	79	15.3	35		5,890	89	75	3,250	3,830	58	2,110	2,060	31
2	33	M.	67	85	17.5	46	5.40	6,170	92	73	3,230	3,330	50	1,740	2,840	42
3	62	M.	87	69	19.3	47	6.08	7,150	82	104	3,650	3,790	44	1,930	3,360	38
4	37	M.	75	81	15.6	38	4.80	7,080	94	87	3,610	4,390	59	2,240	2,690	36
5	62	M.	60	69	16.7	42	5.24	4,930	82	71	2,950	2,860	48	1,710	2,070	34
6	68	M.	54	53	16.1	35	4.05	5,570	103	105	3,520	3,630	67	2,290	1,950	36
7	65	M.	73	64	17.2	46	4.78	5,950	82	93	3,400	3,330	46	1,900	2,620	36
8	61	M.	50	53	14.1	35	4.17	5,020	100	94	3,280	3,260	65	2,130	1,760	35
9	53	F.	63	61	18.6	56	6.86	5,340	85	88	3,340	2,350	37	1,470	2,990	47
10	29	M.	62	61	20.0	47	4.58	6,040	99	99	3,700	3,200	51	1,960	2,837	30
11	52	M.	50	83	14.2	39	4.32	4,920	98	59	3,155	3,000	60	1,920	1,920	38
12	37	M.	51	67	11.5	34	4.80	5,150	92	77	3,180	3,400	66	2,080	1,750	34
Mean values..			64.1	68.7	16.5	42.5	5.02	5,792	92.2	85.4	3,367	3,368	54.1	1,967		37.3
Probable error.....			2.1	2.1	0.5	1.3	0.16	156	1.4	2.7	46	97	1.8	43.5		

volume was 54.1 c.c. for each kilogram of body weight and 1,967 c.c. for each square meter of body surface. The plasma volume for each kilogram of body weight was sharply decreased in two cases (Cases 3 and 9) and increased, that is, 60 c.c. or more, in four cases (Cases 6, 8, 11, and 12).

The volume of cells for each kilogram of body weight varied from 30 to 47 c.c. with a mean value of 37.3 c.c. (normal value for both sexes 36.5 c.c.). In only one case was a high value obtained, 47 c.c.

The arterial and venous blood was studied in seven cases. The oxygen saturation of the arterial blood varied from 83.5 to 93 per cent. There was no correlation between the blood volume or cell volume and the oxygen saturation values. The volume and hemoglobin content of the average individual erythrocyte were calculated according to the method of Haden. The cells were, on the average, of normal size, according to calculated normal values. The hemoglobin in the average cell was definitely increased, 20 per cent above the normal value of Haden.

Comment.—Lemon's data show absence of decisive changes in the total circulating cell volume and blood volume in his cases of chronic arterial anoxemia. The volume status for this group was simple hypervolemia although the mean values were still within the normal range. The mean value for blood volume is approximately 5 c.c. more for each kilogram than the mean for normal persons. The possibility existed that blood volume relative to body weight actually might be increased more than the figures showed; but that the increase might be masked by abnormal body weights for the group. Therefore the blood volume and the plasma volume were calculated for the ideal weight of each subject according to his age, sex, and height. This revealed that the volume values for the ideal weight were slightly lower than the actual values.

The usual response of the blood to lowered oxygen tension has been studied in high altitudes and in experiments with the oxygen chamber. Investigations of this nature, with determinations of the blood volume and plasma volume according to the dye method, have not been carried out, or only for short periods of time at high altitudes; the work of Carrier and his associates,⁹⁸ who studied the response of the blood in high altitudes for only short periods of residence, showed slight or only minimal changes in the total blood volume and plasma volume.

Theoretically the changes in the blood following lowered tension of oxygen in the arterial blood may be (1) increase in the total hemoglobin and cell volume; (2) relative increase in the erythrocytes due to a diminished volume of plasma, and (3) increase in the volume, or hemoglobin content, of the individual erythrocyte. As there were no significant changes in the hemoglobin volume and in the cell volume, concentration of the erythrocytes in the blood together with a lessened volume of plasma was considered. In only two instances (Cases 3 and 9, Table 46) did the data indicate that there was a greater concentration of the erythrocytes; in Case 9 the plasma volume according to body weight was low and the percentage of cells by the hematocrit was markedly elevated. In this case the blood volume according to weight was less than the mean for normal persons, polycythemic hypovolemia. In two cases the cell volume, calculated according to body weight, was high. Concerning the size and hemoglobin content of the average individual erythrocyte, Lemon's studies indicate that although the volume of the cells, according to the calculation methods, was not increased, the hemoglobin content of the individual cell was definitely high.

Harrop has called attention to the fact that the response of the blood to high altitudes and lowered oxygen tension probably

is in two stages: the first response probably is due to shifting of additional cells into the circulation from reservoirs, such as the spleen; the second response comes later and consists in an increase in the number of erythrocytes, due to stimulation of the bone marrow. The response of the erythrocytes in chronic anoxemia of pulmonary origin is variable. Occasionally there is polycythemia, as measured by the concentration of the erythrocytes in the peripheral blood. In no instance was absolute polycythemia present, as measured by determinations of blood volume or of cell volume. In one instance the cell volume for each kilogram of body weight was high, due to a diminished amount of plasma. The most significant change would seem to be an increased amount of hemoglobin in the individual erythrocyte.

The question is frequently raised as to whether polycythemia vera exists or whether the physical signs are the result of anoxemia accompanying chronic pulmonary disease. We have observed the combination of these two conditions; they are not uncommon in older patients. When the two conditions co-exist, the degree of cyanosis is excessive and the oxygen values of the arterial blood in percentage of saturation may be as low as 69.5 (normal 95 to 100). In chronic anoxemia of pulmonary origin, increases in the blood volume had not occurred in any case in sufficient degree to be confused with increases found in polycythemia vera. We believe that increases in the blood volume to 115 or 120 c.c. for each kilogram of body weight, with increased percentage of cells as compared to plasma, rarely, or never, occur as responses of the blood to lowered oxygen tension. Whenever values in excess of these are found, we are of the opinion that they are more likely to represent the condition of true or primary polycythemia, perhaps in an early stage. The basis of cyanosis in polycythemia vera on the one hand, and in the types of polycythemia due to deficient oxygenation

of pulmonary blood on the other, is entirely different. In the primary or true forms of polycythemia, uncomplicated by pulmonary or cardiac disease, the cyanosis, when present, is largely due to reduction in the rate of flow of capillary or venous blood with increased utilization of oxygen, and abnormal exposure of the capillary and venous blood through an increased number of dilated vessels as shown quantitatively by Brown and Sheard. As Lundsgaard and Van Slyke have noted, the increased amount of hemoglobin augments and exaggerates the degree of cyanosis. In the secondary or compensatory types of polycythemia, which occur in some types of pulmonary disease, the cyanosis is due to decreased saturation of the arterial blood with oxygen. Harrop and Heath advanced arguments in favor of the conception that true polycythemia may result from the stimulative effects of anoxemia. The slight or negligible increase in total cell volume and blood volume in cases of chronic emphysema and bronchitis seems to oppose this idea.

PREGNANCY

Keith, Rowntree, and Geraghty studied the blood volume and plasma volume before and after delivery in eleven cases. They found that the volume of blood according to body weight is increased in the later months of pregnancy. The range was from 67 to 115 c.c., averaging 95.6 c.c. for each kilogram of body weight. The plasma volume varied from 38.1 to 72.7 c.c., averaging 58.4 c.c. for each kilogram of body weight. Determinations seven to ten days after delivery indicated an average loss of volume of blood of 1,100 c.c. A loss of 300 c.c. of blood could be accounted for as a result of delivery. The average values after delivery were 90 and 49 c.c. of blood and plasma for each kilogram of body weight. Evidence was not adduced to show the presence of dye in the placenta or amniotic fluid to explain the relatively high volume before delivery.

Koch and Jakobovits, using the dye method, found an average blood volume of 57.3 c.c. for each kilogram of body weight in thirteen normal women. They used Congo-red, and allowed a five-minute period for mixing. There were no obese subjects in the group. These values for normal women are much lower than we and other workers obtained, using the dye method. In twenty-four pregnant women, Koch and Jakobovits found an average volume of 54 c.c. of blood for each kilogram of body weight. Data on the volume of plasma were not given, but their figures for blood volume in normal women, 57.3 c.c., correspond closely to ours for plasma volume, 58.4 c.c., for pregnant women. These values suggest some technical error.

Kaboth, using the dye method, found that the volume of blood of eleven nonpregnant women ranged from 52 to 76 c.c. for each kilogram of body weight. The volume of blood of twenty pregnant women varied from 59.6 to 85 c.c. for each kilogram of body weight. He corrected the pregnant weight by deducting the approximate weight of the fetus. The normal values obtained by these workers are not in accord with the values in nonpregnant and pregnant women obtained by other investigators using the dye method.

There is no unanimity of results in studies on the volume of the blood in pregnancy. The data of Keith, Rowntree, and Geraghty reveal an increased amount of blood and plasma during the later period of pregnancy. Their relative values were higher when correction had been made for the weight of the fetus and amniotic fluid. Their data show an average plasma volume of 58.4 c.c. and an average blood volume of 95.6 c.c. for each kilogram of uncorrected body weight. Following delivery, there was a large decrease in the absolute blood volume, which was greater than could be accounted for by loss of blood at parturition. The average decrease in blood

seven to ten days after delivery was 1,100 c.c. whereas the average loss of blood at delivery was 300 c.c. An increase in the total volume of blood would be expected in pregnancy, because of the fetal circulation. The fact that there is a decrease in the amount of blood following pregnancy in excess of the amount lost by hemorrhage, would seem logical on the basis of Lucas and Dearing's studies. They found that the volume of blood in the newborn infant varied from 330 to 850 c.c. This amount is taken from the maternal circulation. The fetal blood and the amount of blood lost by hemorrhage would account for the difference in blood volume between pregnant and parturient women. This difference was disclosed by Keith and his associates. This study lends confirmation to the belief held in the early part of the nineteenth century that there is a plethora of pregnancy, and confirms the well-known clinical observation of the relatively slight danger of loss of blood in the pregnant woman. In absence of data relating to transportation of dye from maternal to fetal blood a word of caution in the interpretation of such data is necessary. It is possible that pre-edematous states of tissue may be concerned.

HEMORRHAGE AND SHOCK

The studies here presented of blood volume in wound shock and primary hemorrhage have been carried out by Keith⁶¹ in twenty-nine cases as part of his investigations on surgical shock and allied conditions. He noted the phenomena observed in shock to be pallor, thirst, rapid pulse, low blood pressure, and capillary stasis. These are somewhat similar to the symptoms observed in severe anemia. In hemorrhage and shock, however, the erythrocyte counts and unit volume determinations of the erythrocytes do not indicate the degree of anemia that is anticipated. Changes in the blood volume could account for this anomalous observation. Keith found that blood volume and

plasma volume were reduced in soldiers suffering from wound shock and that the degree of reduction in the volume of blood bore a relationship to the severity of the condition. In twenty-seven of twenty-nine cases, the blood volume varied from 50 to 85 per cent of the mean for normal persons as established at that time. The plasma volume was reduced from 62 to 90 per cent of the mean for normal persons. In shock without hemorrhage the blood volume was reduced, but not to the same degree as when hemorrhage had occurred. After moderate hemorrhage there was rapid restoration of the volume of blood. Following acute loss of blood, such as that which was occasioned by withdrawal for use in transfusions, there was rapid restoration in the volume, and the amount restored was largely in the form of plasma. Dreyer and Walker observed the same phenomenon in experimental animals. In cases of severe shock, or of excessive hemorrhage, restoration of fluid failed to occur. Keith found that recovery from wound shock is associated with an increase in the blood volume which may take place with or without the intravenous infusion of blood or of gum saline solution. A significant aim in the treatment of wound shock is to increase the amount of fluid in the circulation.

Robertson and Bock studied the blood volume in fourteen cases of two types of hemorrhage: cases in which the patients were suffering from the late effects of primary hemorrhage, and cases in which they were suffering from secondary loss of blood. With the dye method, they found a reduction in the blood mass to less than 60 per cent of the normal after secondary hemorrhage, and below a certain point, a parallel decrease in the blood pressure. With transfusion and injections of gum acacia, only partial restoration of the volume occurred. Restoration of volume ceased at a point where dilution phenomena would take place. These workers found that with a large fluid intake given

by mouth and by rectum, the blood volume could be markedly increased.

We have no additional work to present on blood volume in shock and hemorrhage. The data of the workers who have been mentioned, using the same methods, are quite in agreement. It seems proved that the blood volume is markedly reduced in shock and hemorrhage, that the mass may be reduced in shock without loss of blood, that the recovery factors in shock and hemorrhage are related to the ability of the blood vessels to retain an adequate amount of fluid in the circulation, and that fluid given by mouth or by rectum, or in the form of transfusions, restores or increases the volume of blood in certain cases of hemorrhage and shock with concomitant improvement in the clinical condition.

Chapter XIV

DISCUSSION OF CLINICAL DATA

Claude Bernard, in his "*Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*," made the following statements: "No one will contest the importance of the study of the various liquids of the organism in normal and pathologic states. It is in fact in the blood, and in the liquids which are derived from it, that one finds the physiologic conditions necessary for the accomplishment of the physiochemical actions of life, and it is in the alteration of these same liquids that the physician searches for the causes of a great number of diseases.

"The progress of modern chemistry has, without a doubt, thrown much light on the composition of animal fluids; nevertheless, the subject still remains surrounded with great obscurity. It does not suffice for the physiologist and the physician to determine more or less exactly the chemical constitution of the organic liquids; it is necessary chiefly to recognize the influence that they exert on the vital manifestations and reciprocally their changes in the diverse organic conditions in the living individual."

Since these statements were written, much has been accomplished along the lines pointed out by Bernard. Progress has been rapid in the chemical and physiochemical investigation of the blood and plasma which constitute the medium of exchange and the intermediary between the internal and external milieu of the organism.

The concentration of the various constituents of the blood, and their fluctuation in health and disease, have been ascertained in many diseases. Blood counts and hemoglobin determinations have become routine and the study of the chemical constituents of the blood has developed and has assumed a position of major importance in clinical medicine. In their quantitative aspects, however, these subjects deal primarily with relative rather than with true values.

We believe that another milestone has been reached; that henceforth in dealing with the blood, concentration studies will fail to suffice and that information concerning total quantities will be demanded in many instances. Such information is easily available now, since the introduction of the dye method. The total blood volume, the plasma volume, and the cell volume can be ascertained readily, without harm to the patient and with an accuracy sufficient for clinical purposes.

To know what changes in blood volume and plasma volume are present and the part they are playing in various diseases may prove all-important to the understanding of disease processes and to the interpretation of their signs and symptoms. Such information as the following is of vital interest to the profession. In polycythemia vera, the blood volume and cell volume may be double or even triple the mean volume for normal persons. The volume of blood as well as the concentration of blood cells is increased. The increase in erythrocytes unquestionably constitutes the fundamental disturbance in this disease, but the increase in total blood volume also is a crucial factor in the signs and symptoms encountered. In certain diseases associated with splenomegaly, the blood volume is in excess of normal, notably in myelogenous leukemia and in cirrhosis of the liver. The plasma volume is usually increased in any form of splenomegaly. This may prove significant in differential diagnosis. An increase in plasma is usually found

also in both the primary and secondary types of anemia. Nephrosis also is characterized by a plasma volume greater than normal. Normal, or even a slightly diminished, blood volume usually is found in hypertension. Increase in blood volume therefore is probably not an important consideration in the pathogenesis of hypertension. The vascular bed is too small for the volume of blood rather than the volume of blood too large for the vascular system. Glomerulonephritis is characterized not by "hydremic plethora" but by a blood volume smaller than the normal. Despite the volume decrease, hypertension is a frequent accompaniment of glomerulonephritis. In myxedema the blood volume and the plasma volume are decreased. The blood volume and plasma volume are decreased in obesity. This is probably exaggerated falsely, if volume values are expressed in terms of body weight. In obesity, blood volume values should be considered relative to body surface rather than to body weight in order to avoid recording a marked decrease in blood and plasma which in part would be apparent rather than real.

That more attention must be directed to the plasma volume in the future is obvious. Moderate increases in plasma volume occur at times in the presence of decreased erythrocytes and apparently this may compensate, in part, for a decrease in erythrocytes. This plasma replacement in anemia may constitute a mechanism for the maintenance of an adequate circulating volume of blood. Replacement is much more complete in cases of anemia with splenomegaly.

In considering blood volume and plasma volume in disease, the range of normal variation must not be overlooked. This is essential to proper interpretation of volume values. Eventually, total blood volume, cell volume, and plasma volume may possibly be recorded in percentage variation from the mean for normal persons which may be designated as zero. If so, the

TABLE 47
VALUES FOR NORMAL PERSONS

	Body weight, kg.	Height, cm.	Body surface.	Age.	Index of fullness.	Hemoglobin.				Blood.				Plasma.				Cells by hematocrit, per cent.	Cell volume for each kg. of body weight.
						Gm. in each 100 c.c.	Total, gm.	Gm. for each kg. of body weight.	Gm. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.	Total volume, c.c.	C.c. for each kg. of body weight.	C.c. for each sq. m. of body surface.				
Range.....	51	154	1.48	17		12.4	563	9.2	368	4,135	66	2,685	2,480	38	1,580	96			
	87	183	2.05	63		20.7	1,616	20.2	808	8,080	107	4,040	4,980	68	2,260	47			
Mean.....	65.9	167.9	1.74	34.8	139	15.7		13.8	508	5,710	87.7	3,278	3,350	51.2	1,920	41	36.5		

normal variation probably will be of the same order of magnitude as that ordinarily accepted in relation to basal metabolism, namely plus or minus 10 per cent.

A parallelism in the changes occurring in the cell volume and plasma volume is not found in health, or in disease. Changes in one do not permit of prediction in regard to variations in total blood volume, in cell volume, and in plasma volume. Hence these factors must be determined individually in each case. The information acquired probably will more than compensate for the effort and time expended.

Chapter XV

SOME SUPPLEMENTARY REMARKS CONCERNING THE PLASMA

Our studies on plasma volume naturally have focused our attention on this very important constituent of the blood. As time has progressed we have become more and more impressed with the important function it serves in the organism. Hence, we have decided to include in this communication a brief chapter on the plasma in health and in disease. We recognize that much of the material in this discussion is somewhat irrelevant to our major thesis of blood volume and plasma volume. Yet it seems desirable to discuss plasma from a somewhat broader point of view in order to indicate the necessity of considering its quantitative aspects in relation to clinical medicine.

The plasma is usually regarded merely as a vehicle for the transportation of erythrocytes. Obviously, its true significance is not realized. What the erythrocyte is to gaseous metabolism, the plasma is to nitrogen, mineral, and water metabolism to some extent. The plasma supplies the fuel; the erythrocytes, the oxygen needed for internal combustion. In a sense, the plasma itself constitutes a liquid fuel.

Many have recognized that plasma should be regarded as a moving tissue, which circulates throughout the body, and which by virtue of its physical properties is permitted unbounded opportunity for chemical activity. As such, it becomes one of the most interesting tissues of the body. Plasma is adapted to the needs of every tissue and cell of the body. It distributes

food, glucose, amino-acids, and lipoids; it carries salts in balanced amounts to maintain osmotic relationships, and it furnishes water as a medium for chemical reaction. It maintains itself in constant acid-base equilibrium and acts also as a buffer. It is also, itself, the seat of chemical reaction and participates in innumerable reactions. It transports hormones and carries the specific products of cells from their seat of origin to their allotted seat of action. It conveys enzymes which work in both the blood and tissues and it collects and removes waste products, conducting them to the appropriate organ of excretion. It gets into and out of capillaries and into and out of the individual cells.

Within itself it carries the materials necessary for repair. When the walls within which the plasma circulates are ruptured or give way, they are automatically and immediately sealed. The plasma also participates in the production, distribution, and dissipation of heat. It also must maintain a marked degree of uniformity both in volume and composition, despite various increments which are constantly being added to it. This is made possible through the organs of excretion. The plasma, therefore, is a marvelous internal medium which in health continuously replenishes and purifies itself and yet maintains itself as a constant both in volume and composition.

With the recognition of these important physiologic functions, further inquiry into the rôle of plasma in pathologic processes naturally follows. Conceptions of disease, since the time of Virchow, have tended to associate interest in pathology with cellular and visceral lesions. Bernard, on the other hand, had strongly indicated the need in medicine for further study of the body fluids, and the pendulum is already beginning to swing back toward Bernard's view. The study of chemical and serologic changes in the blood of necessity deals largely with plasma, or serum. Plasma at least reflects most of the processes

of disease, and in this connection, if in no other, it merits more intensive study. When we realize how great at present is our dependence on qualitative changes in the plasma, how rapidly it has established its just claim to consideration in diagnosis and prognosis, we are led to wonder that so little is known quantitatively concerning it.

We would like to know whether plasma itself is the actual seat of disease, whether there is such a thing as primary diseases of this tissue, or whether changes in the plasma are always secondary. Furthermore, the questions arise whether plasma, as a tissue, is endowed with at least some vital attributes and whether its rôle in disease is active or merely passive. These questions should stimulate inquiry and should eventually become the subject of actual investigation.

In passing, we would raise the question as to whether or not nephrosis may involve the plasma primarily. Nephrosis involves striking deviations from the normal volume and composition of plasma, especially in relation to lipoid and protein content. The limited extent to which nephrosis is primarily a renal disease is now recognized by many investigators.

Discussion of the qualitative changes in the composition of plasma in disease obviously does not belong in this volume. We recognize, however, that such changes do occur in many diseases; in nephrosis, during and subsequent to infectious disease, in multiple myeloma, and in other diseases. Furthermore, quantitative changes in various components of plasma occur in dehydration, after excessive ingestion of water, in uremia, in acidosis, in alkalosis, in hepatic and splenic diseases, in diabetes, in tetany, and in many forms of toxemia. There occur also marked changes in the ratio of plasma to erythrocytes. What concerns us here, most intimately, however, are actual changes in the total amount of circulating plasma which is found in disease.

In this work with values for blood volume, the range for normal persons, as well as the mean, is important, since great fluctuations in volume are not compatible with health or with life. In disease, the number of erythrocytes may be reduced to less than 1,000,000 or even to 500,000 for each cubic millimeter of blood, as in pernicious anemia, or, on the other hand, their number may exceed 10,000,000, as in polycythemia vera. Yet, under either of these conditions, the patient may live; and by proper measures he may be restored to comparative health. Fluctuations of such magnitude in plasma volume are not tolerated. Whereas the range for normal persons in plasma volume is from 40 to 60 c.c.* for each kilogram of body weight, values of 30 c.c. or less for each kilogram of body weight occurred in only five cases and in only twelve was it 35 c.c. or less. These twelve were cases of obesity. The value of 80 c.c. for each kilogram of body weight was exceeded in adults in only five instances, all of which were examples of different forms of splenomegaly. In only twenty-two cases were the figures higher than 75 c.c. for each kilogram of body weight.

The lowest mean group value for plasma in any abnormal condition has been encountered in obesity, 37.3 c.c. for each kilogram of body weight. In this connection, however, the question arises concerning the correctness of expressing plasma volume in relation to body weight. In dehydrated states, however, this objection does not obtain and yet single values as low as 35 c.c. for each kilogram have been encountered. The highest mean values for plasma in human beings have been found in splenomegaly with anemia 68.6 c.c. (Table 25), myelogenous leukemia 69 c.c. (Table 20), hemolytic jaundice

* For practical purposes we kept in mind 40 to 60 c.c. as the limits of the range for normal persons, much as we employed convenient figures for the limits of the range for blood volume for each kilogram of body weight (Table 47).

73.1 c.c. (Table 24). From these observations it can be seen that in certain diseases, fluctuations of considerable magnitude may be encountered. These changes, however, are relatively small in comparison to fluctuations in the concentration of erythrocytes and can almost be attained in animals, under experimental conditions, through the simple expedient either of withholding water or of forcing it to the point of intoxication.

It is our impression that plasma volume may be increased at times as a compensatory or adaptive measure; for instance, to insure larger volume and a fuller vascular system after hemorrhage. This we have regarded as a plasma replacement factor. The volume of the plasma also may undergo quantitative changes in other connections (Fig. 17).

After duly considering the behavior of the plasma in disease, we believe that the plasma volume constitutes one of the most striking and significant so-called constants of the body. Apparently the organism makes every effort to maintain this volume constant within narrow limits. In various types of diseases, deviation from normal occurs at times. Most frequently this indicates failure on the part of the organism. Hence, plasma volume, like blood volume, needs further investigation and must be subjected to actual determination in a large series of cases in order to ascertain its true significance in disease.

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